

# Approaches towards the development of novel asymmetric methodology

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# Approaches towards the Development of Novel Asymmetric Methodology

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Department of Chemistry

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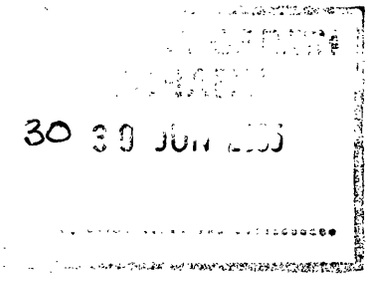
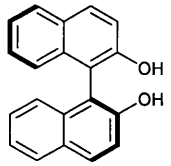


# ABSTRACT

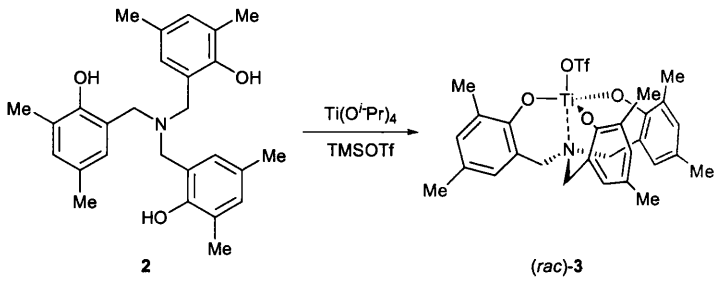
The development of enantioselective transition metal catalysts for asymmetric synthesis continues to demand much attention from the synthetic community.[1] Generally, the introduction of asymmetry into metal-ligand complexes relies on the use of chiral $C_2$-symmetric coordinating ligands, such as (*R*)-BINOL **1** (Figure 1), for the relay of chiral information.[2] The high level of stereocontrol achieved with $C_2$-symmetric ligands has led to many ligands being developed with this symmetry characteristic.[3] However, it has been proposed, for a number of reasons, that transition metal complexes derived from $C_3$-symmetric ligands have even greater potential for asymmetric catalysis than their $C_2$-symmetric counterparts.[4]




(*R*)-BINOL **1**

**Figure 1** *(R)-BINOL **1***

This project is directed towards the development of a new, chiral family of $C_3$-symmetric phenolates as ligands for enantioselective metal catalysed transformations, based on ligand **2**. In order to promote the formation of a configurationally stable, monomeric metal complex, a fourth (nitrogen) donor atom was incorporated in the ligand. Importantly, despite ligand **2** being achiral, it has been demonstrated that it forms a chiral (but racemic) monomeric complex with titanium such as **3** (Scheme 1).[5] This chirality is due to its propeller-like structure, leading to both the *P* and *M* isomers, as can be seen in its X-ray crystal structure (Figure 2).




**2** (*rac*)-**3**

**Scheme 1** *Formation of complex (rac)-**3***

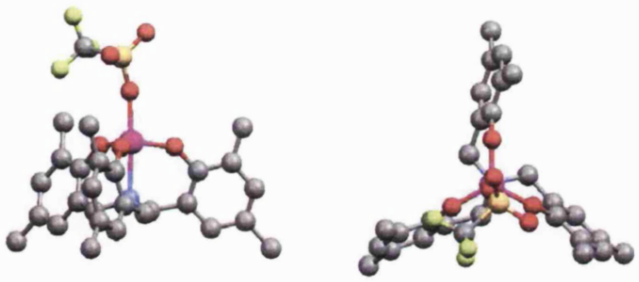
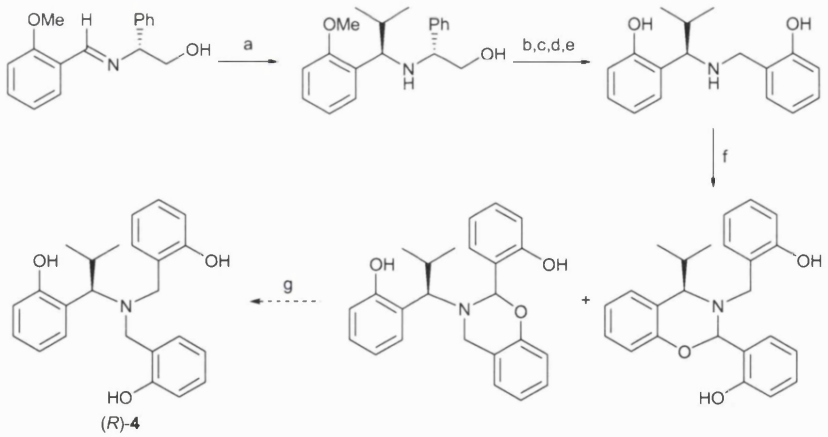


**Figure 2** *Side and top views (left and right respectively) of the X-ray crystal structure of complex (rac)-**3** (only one of two similar molecules found within the asymmetric unit shown and hydrogens omitted for clarity)*

This complex was then screened as a Lewis acid in a range of asymmetric transformations including the *aza*-Diels Alder reaction, diethyl zinc addition to benzaldehyde, allyltributyltin addition to benzaldehyde, the conventional Diels-Alder reaction, and the Aldol reaction. The success in these reactions led to the development and synthesis of a chiral *pseudo*-$C_3$-symmetric ligand (*R*)-**4**, whose chirality would hopefully lock the conformation of the 'propeller-like' complex into one enantiomer. A small amount of (*R*)-**4** appeared to have been synthesised *via* the protocol depicted in Scheme 2 using a chiral auxiliary controlled addition to an imine, reductive amination, and the formation and subsequent cleavage of aminol ethers.




a) $^{i}$PrLi, THF, -85°C, 83%; b) $Pb(OAc)_4$, DCM/MeOH; 6 M HCl 78%; c) 2-methoxybenzaldehyde EtOH, 98%; d) $NaBH_4$, MeOH, 83%; e) $AlBr_3$, toluene, 72%; f) 2-hydroxybenzaldehyde, (*S*)-CSA, DCM, 64%; g) $NaBH_3CN$, TMSCl, MeCN -40°C; KOH, rt, 11%

**Scheme 2** *Synthesis of ligand (R)-**4***

1. I. Ojima, *Catalytic Asymmetric Synthesis*, Wiley VCH, 1993, New York; 2. J. K. Whitesell, *Chem. Rev.*, 1989, **89**, 1581-1590; 3. S. T. Handy, *Curr. Org. Chem.*, 2000, **4**, 363-395; 4. H. Lütjens, G. Wahl, F. Möller, P. Knochel, J. Sundermeyer, *Organometallics*, 1997, **16**, 5869-5878; C. Moberg, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 248-268.; 5. S. D. Bull, M. G. Davidson, A. L. Johnson, D. E. J. E. Robinson, M. F. Mahon, *Chem. Commun.*, 2003, 1750-1751; M. Kol, M. Shamis, I. Goldberg, Z. Goldschmidt, S. Alfi, E. Hayut-Salant, *Inorg. Chem. Commun.*, 2001, **4**, 177-179.

# CONTENTS

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# ABBREVIATIONS

| | |
|---|---|
| Ac | Acetyl |
| APCI | Atmospheric pressure chemical ionisation |
| aq. | Aqueous |
| Ar | Aryl |
| BINOL | 1,1'-Binaphthyl alcohol |
| Bn | Benzyl |
| b.p. | Boiling point |
| br | Broad |
| Bu | Butyl |
| °C | Degrees centigrade |
| CI | Chemical ionisation |
| CSA | 10-Camphorsulphonic acid |
| d | Doublet |
| δ | NMR chemical shift |
| $\delta_{^1H}$ | Proton NMR chemical shift |
| $\delta_{^{13}C}$ | Carbon NMR chemical shift |
| $\delta_{^{19}F}$ | Fluorine NMR chemical shift |
| dba | Dibenzylideneacetone |
| DCC | *N,N'*-Dicyclohexylcarbodiimide |
| 1,2-DCE | 1,2-Dichloroethane |
| DCM | Dichloromethane |
| de | Diastereomeric excess |
| DIPEA | Di-*iso*-propylethylamine |
| DMAP | *N*-Dimethylaminopyridine |
| dr | Diastereomeric ratio |

| | |
|---|---|
| EDC | 1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide |
| ee | Enantiomeric excess |
| EI | Electron ionisation |
| eq. | Equivalent |
| ES | Electrospray |
| Et | Ethyl |
| Ether | Diethyl Ether |
| g | Gram |
| GCMS | Gas chromatography mass spectroscopy |
| *in vacuo* | Under vacuum |
| $^{i}$Pr | *Iso*-propyl |
| IR | Infrared |
| *J* | Coupling constant |
| $\lambda_{max}$ | UV absorption |
| lit. | In the literature |
| liq. | Liquid |
| m | Multiplet |
| M | Molar |
| $M^+$ | Molecular ion |
| *m*-CPBA | *meta*-chloroperbenzoic acid |
| Me | Methyl |
| MEOX | methoxycarbonyl-2-oxyoxazolidinyl |
| mg | Milligram |
| mL | Millilitre |
| mm | Millimetre |
| MOM | methoxymethyl |

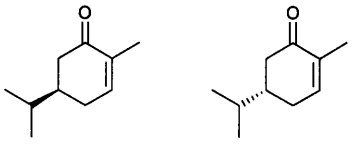
| | |
|---|---|
| m.p. | Melting point |
| m/z | mass/charge ratio |
| NMR | Nuclear magnetic resonance |
| Np | Naphthyl |
| P | Protecting Group |
| PE | Petroleum ether |
| Ph | Phenyl |
| PMB | *para*-methoxybenzyl |
| ppm | Parts per million |
| q | Quartet |
| rt | Room temperature |
| s | Singlet |
| st | Strong |
| t | Triplet |
| TBDPS | *tert*-butyl diphenylsilyl |
| TBHP | *tert*-butyl hydroperoxide |
| TBS | *tert*-butyl dimethylsilyl |
| $^{t}$Bu | Tertiary Butyl |
| TES | Triethylsilyl |
| Tf | Trifluoromethyl sulfonate |
| THF | Tetrahydrofuran |
| TIPS | tri-*iso*-propyl silyl |
| TLC | Thin layer chromatography |
| UV | Ultra violet |
| υ | Frequency |
| w | Weak |

# CHAPTER 1:
# *Introduction*

# 1 INTRODUCTION

1 INTRODUCTION

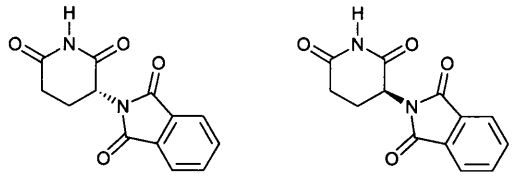
The biological activity of an active molecule or 'drug' is the result of its interaction with chiral because they are assemblies of several units containing one or more stereogenic centre, such as amino acids, carbohydrates, and lipids. Thus, the two enantiomers of a racemic drug have the potential to interact with the targeted bio-receptor differently, each causing a potentially different biological effect. For example, the two enantiomers of carvone interact with nasal bio-receptors in distinctive ways with (+)-carvone (*R*)-**1** smelling of spearmint, whilst (-)-carvone (*S*)-**1** smells of caraway seeds (Figure 1).




(*R*)-carvone **1** (*S*)-carvone **1**

**Figure 1** *Carvone* ***1***

An infamous example of where one enantiomer of a drug had devastating effects, whilst the other was beneficial, is the use of the drug thalidomide **2** (Figure 2) that was prescribed to pregnant women during the 1960s to help prevent morning sickness. Unfortunately, it was later discovered that many of the babies were born with malformed limbs; further investigation revealed that (*R*)-(+)-thalidomide (*R*)-**2** had the positive effects of stopping morning sickness, whereas (*S*)-(-)-thalidomide (*S*)-**2** had teratogenic properties which damaged the foetus.[1] Unfortunately, in this case it was subsequently revealed that thalidomide is racemised in the body, meaning that the administration of only the (*R*)-enantiomer would still have resulted in these tragic consequences; however, it still clearly demonstrates the importance of synthesising a drug in its enantiomerically pure form.




(*R*)-(+)-thalidomide **2** (*S*)-(-)-thalidomide **2**

**Figure 2** *Thalidomide* ***2***

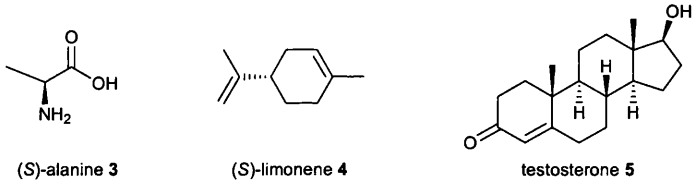
## 1.1 Asymmetric Synthesis

There are four main ways to synthesise an enantiomerically pure compound:

- The chiral pool approach
- Resolution of a racemate
- The use of chiral auxiliaries
- Asymmetric catalysis.

### 1.1.1 The Chiral Pool Approach

Using the chiral pool is a very popular approach towards the synthesis of enantiomerically pure molecules, involving the use of chiral starting materials derived from a naturally occurring product. Typical sources for the chiral pool are amino acids, terpenes, and steroids (examples of which are depicted in Figure 3).

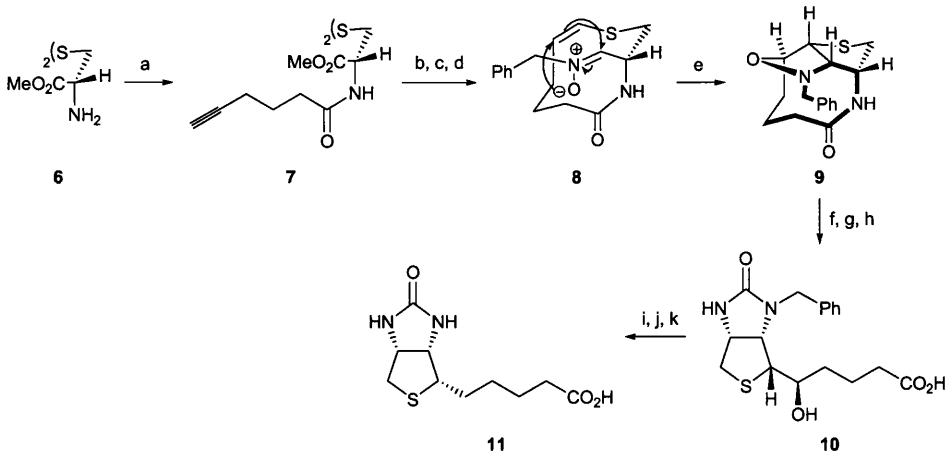



(*S*)-alanine **3** (*S*)-limonene **4** testosterone **5**

**Figure 3** *(S)-Alanine **3**, (S)-limonene **4**, and testosterone **5**: an amino acid, a terpene, and a steroid respectively*

For example, the synthesis of (+)-biotin **11**, an essential vitamin, from L-cystine, a readily available member of the chiral pool, was reported by Baggiolini *et al.* in 1982.[2] Highlights of the synthetic scheme are depicted in Scheme 1. This elegant, enantiospecific synthesis takes advantage of the stereochemistry of the starting material to first control the cyclisation of **7** to form a 10-membered ring, and consequently the [3+2] nitrone-alkene cycloaddition reaction of this ring system to give a single stereoisomer **9**. The synthesis begins with L-cystine dimethyl ester **6**, which undergoes acylation of its primary amino group with 5-hexynoyl chloride to give amide **7**. This is then converted into nitrone **8** by first reducing the disulphide bond with Zn dust in acetic acid. When this reaction is carried out in the presence of air, the newly formed thiol reacts spontaneously with the terminal acetylene in an intramolecular process. Nitrone **8** is obtained *via* partial reduction of the methyl ester followed by treatment of the newly formed aldehyde with benzylhydroxylamine hydrochloride. The formation of the 10-membered ring restricts the mobility of the alkene in space, forcing the ensuing nitrone-alkene addition reaction to proceed through a transition state that leads to the

formation of **9** exclusively. (+)-Biotin **11** is subsequently obtained following reductive cleavage of the N-O bond, selective hydrolysis of the derived lactam and removal of the nitrogen and the hydroxyl protecting groups.




a) 5-hexynoyl chloride, pyr., DCM, 0°C, 90% yield; b) Zn dust, AcOH, 65% yield; c) $^{i}Bu_2AlH$, toluene, -78°C, 95% yield; d) BnNHOH.HCl, DCM, 72% yield; e) BaO, reflux, toluene; f) Zn dust, AcOH/$H_2O$, 70°C; g) $ClCO_2Me$, THF/2$nNa_2CO_3$, 0°C, 65% yield over 2 steps; h) $Ba(OH)_2$, dioxane/$H_2O$, 87% yield; i) $SOCl_2$, $Et_2O$, 68% yield; j) $NaBH_4$, DMF, 80°C, 76% yield; k) HBr (aq.), 85% yield

**Scheme 1** *The synthesis of (+)-biotin **11** from L-cystine*

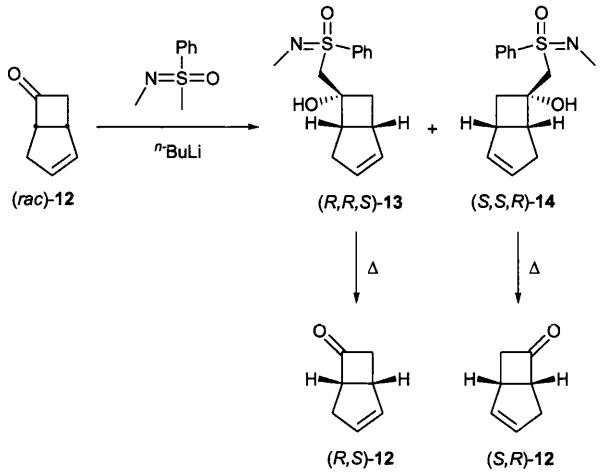
The obvious limitation of the chiral pool approach arises from the availability of the starting material which may be expensive and/or difficult to obtain. The synthetic route must also be adjusted to the starting material; very often several extra functional group interconversions are required to remove redundant functionalities, thereby lengthening the synthetic protocol. Starting materials from the chiral pool are frequently only available as a single enantiomeric series, which is often prohibitive, although this drawback can be addressed in certain circumstances by protocols that selectively invert the configuration of specific stereocentres.

## 1.1.2 Resolution of Racemates

### Resolution *via* the Formation of Diastereomers

This is a process whereby a chiral resolving agent is employed to separate the enantiomers of a racemic mixture. Conversion to diastereomers which exhibit different chemical properties enables their separation by fractional crystallisation or chromatography. This approach requires the use of a stoichiometric amount of an often expensive resolving agent. A typical example is the resolution of a racemic mixture of bicyclic ketone **12** *via* its reaction with *N,S*-dimethyl-*S*-phenylsulfoximine to form two

diastereomers **13** and **14** (Scheme 2), which can be easily separated by flash chromatography.[3]

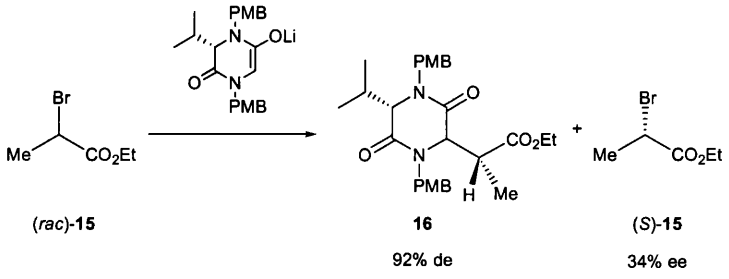



**Scheme 2** *Resolution of cyclic ketone (rac)-***12**

The maximum yield that can be obtained from this process is only 50%, meaning that costs can be prohibitive because half of the material is discarded and the resolving agent cannot always be recovered. Nevertheless, this approach is still one of the most effective approaches employed by industry for chiral synthesis on a large scale.

### Kinetic Resolution[4]

This type of strategy combines a resolution of a racemate with an asymmetric reaction and relies on the different reaction rates of the enantiomers with an enantiomerically pure reagent or catalyst. Ideally, the difference in the reaction rates is such that one enantiomer reacts readily with the chiral reagent/catalyst, whilst the other is essentially inert. Separation of the compounds would then be possible affording the two pure enantiomers. This process is illustrated in Scheme 3: one enantiomer of a racemic mixture of an α-bromo ester **15** reacts with a chiral auxiliary giving the diastereomer **16** in 92% de and the unreacted enantiomer (*S*)-**15** in 34% ee.[5]

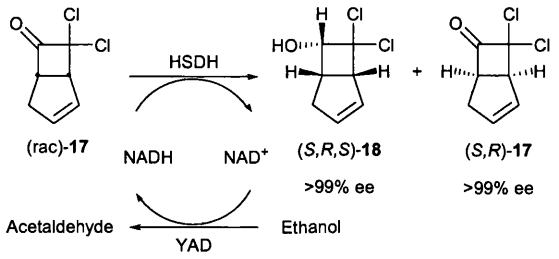



**Scheme 3** *Kinetic resolution using an enantiomerically pure reagent*

However, it also suffers inherent drawbacks: the maximum possible yield is 50% and the enantiomeric purity of the recovered substrate and product is affected by the extent of conversion. This is due to the fact that the selectivity towards a particular enantiomer is under kinetic control. Initially both the enantiomers are of equal concentration, however, as the kinetically favourable enantiomer is consumed the relative concentration of the unfavourable enantiomer increases until it exists in a high excess. Thus, a point will eventually be reached where the statistical weight of the kinetically less reactive enantiomer will become the dominant factor, hence decreasing the selectivity towards the kinetically favoured enantiomer. This will result in the unfavourable enantiomer reacting, leading to a lowering of the overall enantiomeric excess.

### Enzymatic Resolution

Enzymes offer a powerful alternative as they are catalytic and perform clean and specific reactions to afford chiral products in very high ee. A representative example, using 3α,20β-hydroxysteroid dehydrogenase (HSDH) enzyme and nicotinamide adenine dinucleotide (NADH) as the reducing agent, to reduce the activated α,α-dichloro-ketone (*rac*)-**17** is depicted in (Scheme 4).[6] In the process of reducing one enantiomer of ketone (*rac*)-**17** to the secondary alcohol (*S,R,S*)-**18**, NADH is oxidised to $NAD^+$ which results in stoichiometric consumption of this expensive cofactor. However, to circumvent this problem yeast alcohol dehydrogenase (YAD) was successfully used to regenerate the NADH, using ethanol as a sacrificial oxidant. This process yields the unreacted enantiomer (*S,R*)-**17** and the secondary alcohol (*S,R,S*)-**18** both in >99% ee.




**Scheme 4** *The reduction of an activated α,α-dichloro-ketone (rac)-**17** with HSDH and NADH.*

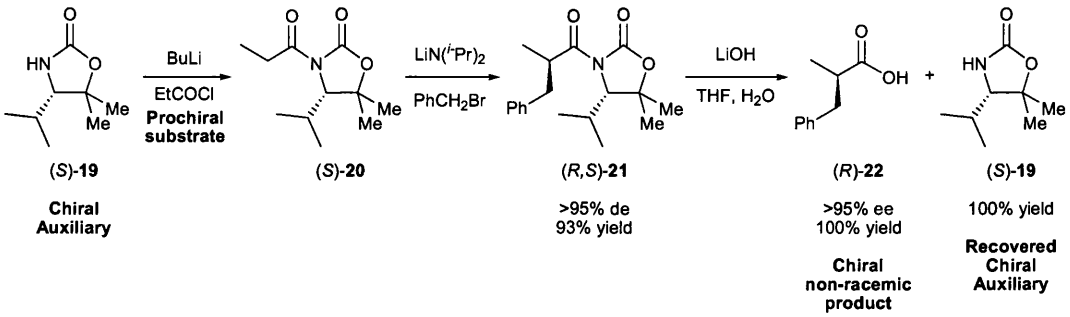
Unfortunately, enzymes are expensive and often highly substrate specific. Furthermore, they show a strong sensitivity to their environment and often only perform a transformation under very specific experimental conditions. Normally enzymes function in an aqueous environment and at a specific temperature; any variations to this

can cause denaturisation of the enzyme. As a consequence, they tend to be insoluble in organic solvents; therefore a biphasic system is required, complicating the reaction process.

### 1.1.3 Chiral Auxiliaries

In the chiral auxiliary approach, a prochiral starting reagent is first attached to an enantiomerically pure auxiliary. A reaction is then performed at the prochiral centre to introduce a new stereogenic centre. The two products are now diastereomeric, with one being preferentially formed. The major product can then be easily isolated following usual chromatographic or recrystallisation methods and the chiral auxiliary is then cleaved to afford the enantiomerically pure product. This method often affords high levels of diastereoselectivity rendering separation of the major and minor diastereomeric products even easier. A stoichiometric chiral auxiliary must facilitate easy and efficient attachment to the prochiral reagent, exhibit absolute control over the stereoselectivity in subsequent reactions on the attached substrate and be readily removed. The chiral auxiliary must also be able to be efficiently recycled, unless it is very inexpensive, in which case it can be destroyed in the cleavage step.

The use of SuperQuat auxiliary (*S*)-**19**, developed by Davies *et al.* is an example of 'chiral auxiliary' controlled enolate alkylation (Scheme 5).[7] The chiral auxiliary oxazolidinone shields the lower face of the enolate of (*S*)-**20** and directs the alkylation reaction completely to the upper face (as drawn). This exclusively affords the alkylated product (*R,S*)-**21** which, when the chiral auxiliary is removed, yields the product (*R*)-**22** in a quantitative yield and high enantiomeric excess.




**Scheme 5** *The use of the SuperQuat chiral auxiliary (S)-**19***

The main disadvantage to this approach is the necessity to perform two extra steps in the synthesis in order to introduce and remove the auxiliary, which should be recyclable.

### 1.1.4 Asymmetric Catalysis

Asymmetric catalysis, however, seems the ideal solution for the preparation of chiral molecules since it only requires a small amount of an often expensive chiral catalyst to perform the asymmetric transformation. The asymmetric catalyst modifies the course of the reaction leading to diastereomeric transition states that are different in energy, thus enabling a chiral product to be formed in very high enantiomeric excess.

This can be understood by considering the example of the reduction of a prochiral ketone. In an achiral environment (i.e. using an achiral reducing agent) attack of the nucleophile at the *re-* and *si-* faces of the carbonyl occurs *via* enantiomeric transition states to afford a racemic product (Figure 4).

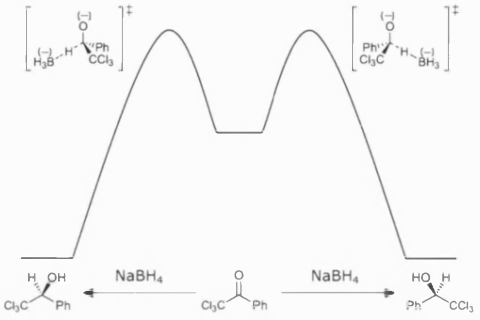



**Figure 4** *Nucleophilic attack in an achiral environment*

However, when a chiral catalyst is introduced, the whole system becomes chiral. Therefore, the transition states are now diastereomeric and so, relative to each other, have different energies (Figure 5). Thus, the reaction has the potential to produce the enantiomers in unequal amounts because the pathway with the lower energy will now be kinetically favoured. In this particular case the chiral alcohol obtained by the enantioselective CBS reduction of 2,2,2-trichloro-1-phenylethanone, was afforded in >98% ee.[8]

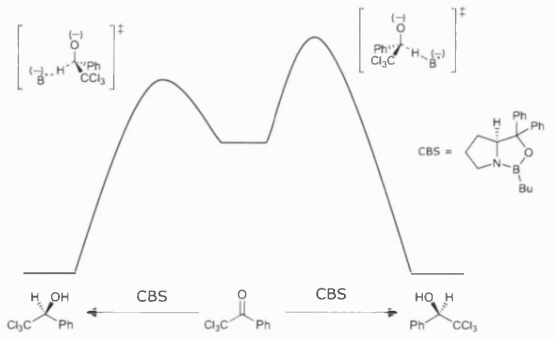



**Figure 5** *Nucleophilic attack in a chiral environment*

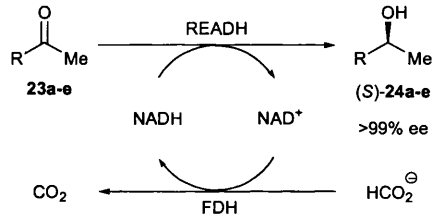
Unfortunately, catalysts are often highly substrate specific and so are not always universal. Therefore, for each enantioselective reaction to be performed and for each class of substrates a new catalyst often has to be developed and optimised.

There are three main methods of asymmetric catalysis:

- The use of enzymes
- Organocatalysis
- Organometallic catalysis.

### Enzymatic Asymmetric Catalysis

As mentioned in the resolution section (1.1.2), the use of enzymes is a powerful catalytic method and their synthetic applications result in chiral products with very high enantioselectivity. A recent example is the use of (*S*)-alcohol dehydrogenase from *Rhodococcus erythropolis* (READH) using NADH as a reductant to reduce a range of ketones **23a-e**.[9] NADH is regenerated from $NAD^+$ using formate dehydrogenase from *C. boidini* (FDH). This process results in chiral (*S*)-alcohols **24a-e** in >99% ee and >95% conversion.




**Scheme 6** *Application of READH in the reduction of a range of ketones* ***23a-e***

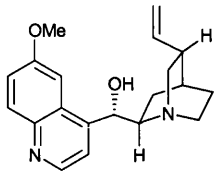
**Table 1**

| Product | R | Conversion /% | ee /% |
|---|---|---|---|
| **24a** | Ph | >95 | >99 |
| **24b** | 4-Cl($C_6H_4$) | >95 | >99 |
| **24c** | $CH_2CO_2CH_2CH_3$ | >95 | >99 |
| **24d** | $(CH_2)_4CH_3$ | >95 | >99 |
| **24e** | $(CH_2)_5CH_3$ | >95 | >99 |

### Organocatalysis

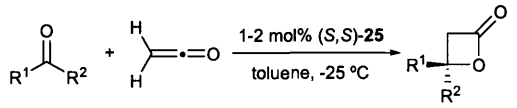
Organocatalysis is the use of chiral organic molecules as catalysts in asymmetric transformations and is a rapidly expanding area of catalysis, with applications in phase transfer catalysis, kinetic resolution, and asymmetric synthesis.[10] A seminal example is

the use of cinchona alkaloid, quinidine (*S,S*)-**25** to synthesise β-lactones (*R*)-**28a-g**, reported by Wynberg *et al.* in 1985 (Scheme 7, Table 2).[11] The [2 + 2] cycloaddition between a range of aldehydes and ketenes was successfully catalysed by quinidine (*S,S*)-**25**, to afford lactones (*R*)-**28a-g** in good enantioselectivities (89-98%).




(*S,S*)-**25**

**Figure 6** *Cinchona alkaloid quinidine (S,S)-**25***




**26** **27** (*R*)-**28a-g**

**Scheme 7** *[2+2] Cycloaddition catalysed by quinidine (S,S)-**25***

**Table 2**

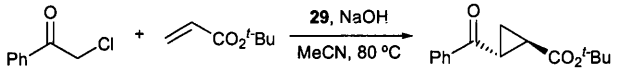
| Lactone | $R^1$ | $R^2$ | Yield /% | ee /% |
|---|---|---|---|---|
| **28a** | $CCl_3$ | H | 89 | 98 |
| **28b** | $CCl_2CH_3$ | H | 95 | 91 |
| **28c** | $CCl_2CH_2CH_3$ | H | 87 | 89 |
| **28d** | $CCl_2(C_6H_4)$ | H | 89 | 90 |
| **28e** | $CCl_3$ | $CH_3$ | 72 | 94 |
| **28f** | $CCl_3$ | 4-Cl($C_6H_4$) | 68 | 90 |
| **28g** | $CCl_3$ | 4-$NO_2$($C_6H_4$) | 95 | 89 |

In 2003, Ley *et al.* reported the use of 1,4-diaza-bicyclo[2.2.2]octane (DABCO) **29** (Figure 7) as a organocatalyst for the one-pot diastereoselective cyclopropanation of a range of acyl chlorides with acrylates *via* an ammonium ylide, resulting in the cyclopropane products in good yields and diastereoselectivity.[12] For example, the reaction of 2-chloro-1-phenylethanone **30** with *tert*-butyl acrylate **31** in the presence of one equivalent of DABCO **29** and sodium hydroxide, resulted in *trans-tert*-butyl 2-benzoylcyclopropane carboxylate **32**, in >95:5 dr (*trans:cis*) and 79% yield (Scheme 8, Table 3, entry 1). DABCO was chosen as a mimic for the core structure of cinchona alkaloids, which have the potential to catalyse the enantioselective cyclopropanation. The process was also shown to be catalytic, with *trans*-**32** being obtained in >95:5

diastereomeric ratio and 69% yield, when 2-chloro-1-phenylethanone **30** was treated with *tert*-butyl acrylate **31** in the presence of 20 mol% of DABCO (Table 3, entry 2).

**29**

**Figure 7** *1,4-Diaza-bicyclo[2.2.2]octane (DABCO)* ***29***



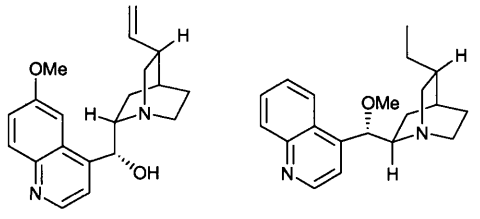

**30** **31** *trans*-**32**

**Scheme 8** *Cyclopropanation of* ***30*** *with tert-butyl acrylate catalysed by DABCO* ***29***

**Table 3**

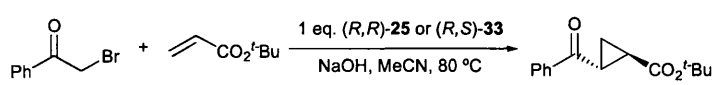
| Entry | Catalyst mol% | Yield /% | *trans* : *cis* |
|---|---|---|---|
| 1 | 100 | 79 | >95 : 5 |
| 2 | 20 | 69 | >95 : 5 |

Cinchona alkaloids (*R*,*R*)-**25** and (*R*,*S*)-**33** (Figure 8) were then applied as organo-catalysts for the stoichiometric one-pot enantioselective cyclopropanation of 2-bromo-1-phenylethanone **34** with *tert*-butyl acrylate **31** (Scheme 9, Table 4).[12] For example, this reaction in the presence of alkaloid (*R*,*R*)-**25** resulted in the cyclopropane product *trans*-(+)-**32** in 94% ee and 57% yield (Table 4, entry 1). Use of (*R*,*S*)-**33** afforded *trans-tert*-butyl 2-benzoylcyclopropanecarboxylate **32** as the opposite enantiomer (-)-**32** in a similar yield and enantioselectivity (58% yield, and 94% ee) (Table 4, entry 2). It was found that 2-chloro-1-phenylethanone **30** did not react under these conditions.



(*R*,*R*)-**25** (*R*,*S*)-**33**

**Figure 8** *Chinchona alkaloids (R,R)-****25*** *and (R,S)-****33***



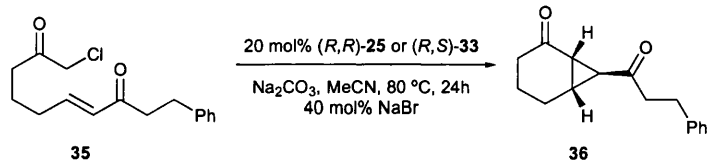

**34** **31** *trans*-**32**

**Scheme 9** *Enantioselective cyclopropanation of* ***34*** *with tert-butyl acrylate* ***31*** *catalysed by cinchona alkaloids (R,R)-****25*** *and (R,S)-****33***

**Table 4**

| Entry | Catalyst | Yield /% | ee /% |
|---|---|---|---|
| 1 | (*R*,*R*)-**25** | 57 | 94 (+) |
| 2 | (*R*,*S*)-**33** | 58 | 94 (-) |

In 2004, Ley *et al.* reported the application of these cinchona alkaloids in the enantioselective organo-catalytic intramolecular cyclopropanation of alkenyl α-chloroketone **35** (Scheme 10, Table 5), with DABCO having been used to optimise the conditions.[13] Treatment of (*E*)-1-chloro-10-phenyldec-6-ene-2,8-dione **35** with 20 mol% of (*R*,*R*)-**25** in the presence of 40 mol% NaBr, resulted in the bicyclic product (+)-**36** in 94% ee and 61% yield (Table 5, entry 1). It was found that without the addition of NaBr, the reaction proceeded much more slowly, requiring 96 hours and affording the bicyclic product (+)-**36** in only 64% ee (Table 5, entry 2). It was therefore proposed that the addition of NaBr facilitated the formation of the intermediate quaternary ammonium salt of the alkaloid, thus accelerating the reaction rate. Using amine (*R*,*S*)-**33** the opposite enantiomer of the cyclopropane product was formed in 94% ee (Table 5, entry 3).




35 36

**Scheme 10** *Intramolecular cyclopropanation of alkenyl α-chloroketone* ***35*** *catalysed by cinchona alkaloids (R,R)-**25** and (R,S)-**33***

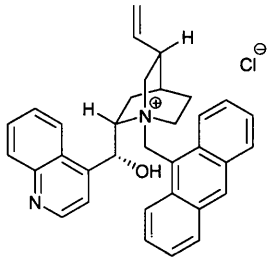
**Table 5**

| Entry | Catalyst | Yield /% | ee /% |
|---|---|---|---|
| 1 | (*R*,*R*)-**25** | 61 | 94 (+) |
| 2[a] | (*R*,*R*)-**25** | 67 | 64 (+) |
| 3 | (*R*,*S*)-**33** | 48 | 94 (-) |

[a] Without addition of NaBr, reaction time 96 h.

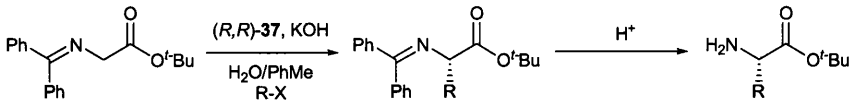
In 1997, Lygo *et al.*[14] and Corey *et al.*[15] independently reported the use of a quaternary ammonium asymmetric phase transfer catalyst (PTC) derived from cinchona alkaloids, both of which were used for the alkylation of the enolate derived from *tert*-butyl glycinate-benzophenone **38**. The catalyst, (*R*,*R*)-**37**, reported by Lygo *et al.* is depicted in Figure 9 and was applied to enolate alkylations using a range of alkyl halides, resulting in the alkylated imines in good enantioselectivities (Scheme 11, Table 6).

Only the yields and enantioselectivities of the amino esters **40a-f** were reported as the intermediate imines were found to be difficult to purify.



(*R,R*)-**37**

**Figure 9** *Quaternary ammonium PTC (R,R)-**37** reported by Lygo et al.*



**38** **39a-f** **40a-f**

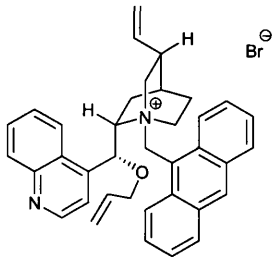
**Scheme 11** *Application of Lygo's PTC catalyst (R,R)-**37** in the alkylation of **38***

**Table 6**

| Product | R-X | Yield of 40 /% | ee of 40 /% |
|---|---|---|---|
| **40a** | $CH_3I$ | 41 | 89 |
| **40b** | $CH_3(CH_2)_3I$ | 42 | 88 |
| **40c** | $CH_2{=}CHCH_2Br$ | 76 | 88 |
| **40d** | $PhCH_2Br$ | 68 | 91 |
| **40e** | (2-naphthyl)$CH_2Br$ | 75 | 86[a] |
| **40f** | $^{t}BuO_2CCH_2I$ | 84 | 72[a] |

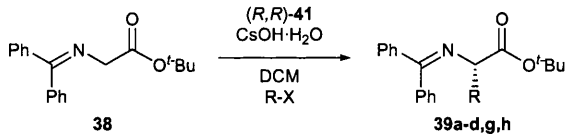
[a] Ee of crude *N*-benzoylamino acid *tert*-butyl ester derivative, determined by HPLC

Phase transfer catalyst (*R,R*)-**41** reported by Corey *et al.* was used for the same transformation under slightly different conditions and resulted in the alkylated imines in higher enantioselectivities (Scheme 12, Table 7).



(*R,R*)-**41**

**Figure 10** *Quaternary ammonium PTC (R,R)-**41** reported by Corey et al.*

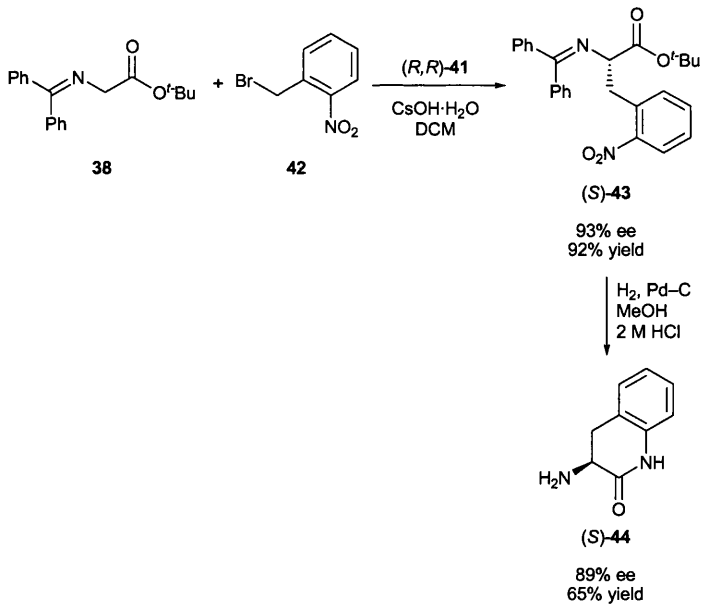



**Scheme 12** *Application of Corey's PTC catalyst (R,R)-**41** in the alkylation of **38***

**Table 7**

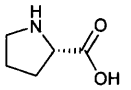
| Product | R-X | Yield /% | ee /% |
|---|---|---|---|
| **39a** | $CH_3I$ | 71 | 97 |
| **39b** | $CH_3(CH_2)_3I$ | 82 | 98 |
| **39c** | $CH_2=CHCH_2Br$ | 89 | 97 |
| **39d** | $PhCH_2Br$ | 87 | 94 |
| **39g** |  | 75 | 99 |
| **39h** | $Ph_2CHBr$ | 73 | >99 |

The application of phase transfer catalyst (*R*,*R*)-**41** has been reported in the synthesis of (*R*)- and (*S*)-3-amino-3,4-dihydro-1*H*-quinolin-2-one **44** in high yield and enantiomeric excess, which are valuable building blocks for the synthesis of biologically active agents.[16] The synthesis of (*S*)-**44** is depicted in Scheme 13. Alkylation of *tert*-butyl glycinate-benzophenone **38** with 2-nitrobenzyl bromide **42** afforded the 2-nitro phenylalanine derivative (*S*)-**43** in 93% ee and 92% yield. This was followed by catalytic hydrogenation under acidic conditions to result in the one-pot reduction of the nitro group, deprotection of the amine and carboxyl functionalities and cyclisation to result in (*S*)-**44** in 89% ee and 65% yield.



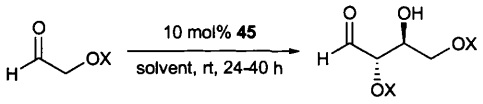

**Scheme 13** *Synthesis of (S)-3-amino-3,4-dihydro-1H-quinolin-2-one **44***

Organocatalysis has more recently been applied to the aldol reaction. An important example of this is the enantioselective direct aldol reaction of α-oxyaldehydes **46a-e** catalysed by L-proline **45** (Figure 11), providing a facile route to polyols.[17] In the presence of 10 mol% of L-proline **45** the di-protected triols **47a-e** were afforded in excellent enantioselectivities (95-98%), moderate to good yields (42-92%) and ≥ 4:1 *anti*:*syn* selectivity (Scheme 14, Table 8). The best results were obtained with those α-oxyaldehydes with relatively electron rich oxyalkyl groups such as benzyl (**46a**: X = Bn; 98% ee, 73% yield) (Table 8, entry 1) and *para*-methoxybenzyl (**46d**: X = PMB; 97% ee, 85% yield) (Table 8, entry 4). Bulky α-silyl protecting groups were also found to undergo the reaction with very high enantioselectivity with the tri-*iso*-propylsilyl di-protected triol **47b** (X = TIPS) being produced in 95% ee and 92% yield (Table 8, entry 3).




45

**Figure 11** *Organocatalyst L-Proline* ***45***




**46a-e** **(*S*,*S*)-47a-e**

**Scheme 14** *L-Proline catalysed aldol reaction of α-oxyaldehydes* ***46a-e***

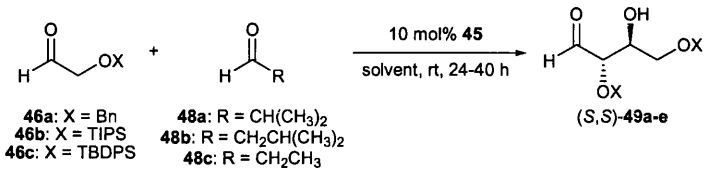
**Table 8**

| Entry | Product | X | Solvent | Yield /% | *anti* : *syn* | ee /% |
|---|---|---|---|---|---|---|
| 1 | **47a** | Bn | DMF | 73 | 4 : 1 | 98 |
| 2 | **47b** | TIPS | DMSO | 92 | 4 : 1 | 95 |
| 3 | **47c** | TBDPS | DMF/dioxane | 61 | 9 : 1 | 96[a] |
| 4 | **47d** | PMB | DMF | 64 | 4 : 1 | 97 |
| 5 | **47e** | MOM | DMF | 42 | 4 : 1 | 96 |

[a] Using 20 mol% of the catalyst

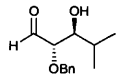
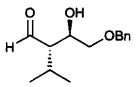
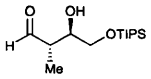
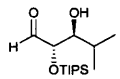
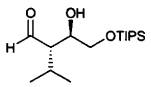
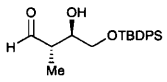
This process was also extended to the cross-aldol reaction between α-oxyaldehydes and α-alkylaldehydes, producing mono-protected *anti*-1,2-diols **49a-e** in excellent enantiomeric excesses (94-99%) and poor to good yields (33-84%) (Scheme 15, Table 9). It was found that in the presence of alkylaldehydes with enolisable α-protons, the α-oxyaldehydes invariably acted as the electrophile. A representative example is the reaction between propionaldehyde **48c** and TBDPS protected glycoaldehyde **46c**,

affording the product **49f** in 99% ee and 84% yield (Table 9, entry 6). The roles of the aldehydes were reversed when an aldehyde with a bulky alkyl group was used, though the products were obtained in the lowest yields. For example, the cross-aldol reaction between *iso*-butyraldehyde **48b** and TIPS-protected glycoaldehyde **46b** resulted in (2*S*,3*S*)-3-hydroxy-4-methyl-2-(tri-*iso*-propyl silyloxy) pentanal **49d** in 99% ee, but only 43% yield (Table 9, entry 4).




**Scheme 15** *L-Proline catalysed crossed aldol reaction of α-oxy and alkyl aldehydes **46a-c** and **48a-c***

**Table 9**

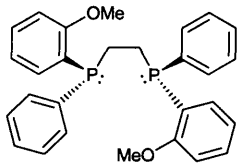
| Entry | X | R | Product | Yield /% | *anti* : *syn* | ee /% |
|---|---|---|---|---|---|---|
| 1 | Bn | $CH(CH_3)_2$ |  **49a** | 33 | 7 : 1 | 96 |
| 2 | Bn | $CH_2CH(CH_3)_2$ |  **49b** | 64 | 4 : 1 | 94 |
| 3 | TIPS | $CH_2CH_3$ |  **49c** | 75 | 4 : 1 | 99 |
| 4 | TIPS | $CH(CH_3)_2$ |  **49d** | 43 | 8 : 1 | 99 |
| 5 | TIPS | $CH_2CH(CH_3)_2$ |  **49e** | 54 | 4 : 1 | 99 |
| 6 | TBDPS | $CH_2CH_3$ |  **49f** | 84 | 5 : 1 | 99 |

Organocatalysts are generally more tolerant of water than their organometallic counterparts. They also have the advantage over enzymes that they can be used in a variety of organic solvents and are more widely applicable. However, as this field of research is still relatively new, organocatalysis does not yet rival the scope of reactions of organometallic catalysis, or the efficiency and selectivity of enzymes.

### Organometallic Catalysis

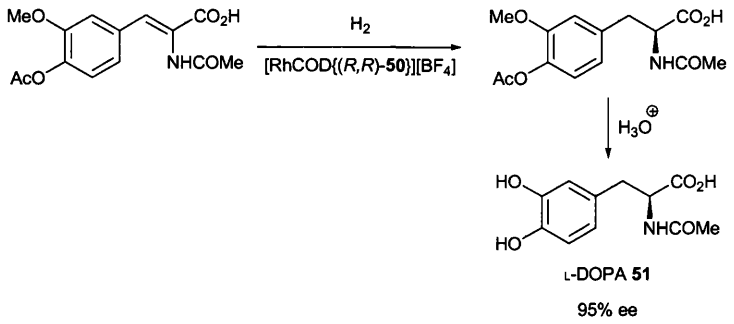
Organometallic catalysis is the use of metal based complexes to catalyse an asymmetric process and is the most commonly used method in asymmetric catalysis, for a wide range of transformations. In 2001 the Nobel prize was awarded to Dr William S. Knowles, Professor Ryoji Noyori, and Professor K. Barry Sharpless, for *"their development of catalytic asymmetric synthesis"*.[18] Knowles and Noyori received the Prize for *"their work on chirally catalysed hydrogenation reactions"* whilst Sharpless received his award for *"his work on chirally catalysed oxidation reactions"*. These advances in asymmetric catalysis have had a remarkable impact on research and novel drug synthesis, and a number of highlights will now be described.

The rhodium(III) complex of diphosphine ligand (*R,R*)-Di-PAMP **50** (Figure 12), developed by Knowles *et al.* in 1977,[19] has been applied on a industrial scale to the synthesis of L-DOPA **51**, which is a drug used for the treatment of Parkinson's disease (Scheme 16).[20] This was the first industrial use of a chiral transition metal complex for asymmetric synthesis.




**50**

**Figure 12** *Diphosphine ligand, (R,R)-Di-PAMP* ***50***



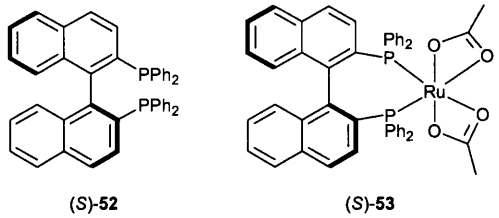

L-DOPA **51**

95% ee

**Scheme 16** *Synthesis of L-DOPA* ***51*** *using a rhodium complex of (R,R)-Di-PAMP* ***50***

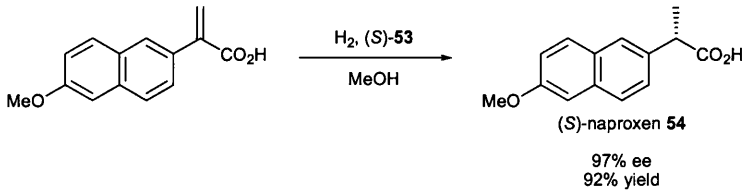
In 1980 Noyori *et al.* developed a chiral diphosphine ligand, BINAP **52** (Figure 13), which was found to be an excellent ligand for rhodium catalysed reactions.[21] However, it was found that ruthenium(II) BINAP complex (*S*)-**53** was a highly selective catalyst for the hydrogenation of α,β and β,γ-unsaturated carboxylic acids, resulting in products in a much higher enantioselectivity than when using the rhodium catalyst.[22] An

example is the synthesis of the anti-inflammatory agent (*S*)-naproxen **54** using [Ru(OCOCH$_3$)$_2$\{(*S*)-BINAP\}] **53** (Figure 13), in 97% ee and 92% yield (Scheme 17).




(*S*)-**52** (*S*)-**53**

**Figure 13** *Diphosphine ligand (S)-BINAP* ***52*** *and its Ru(II) complex [Ru(OCOCH$_3$)$_2$\{(S)-BINAP\}]* ***53***

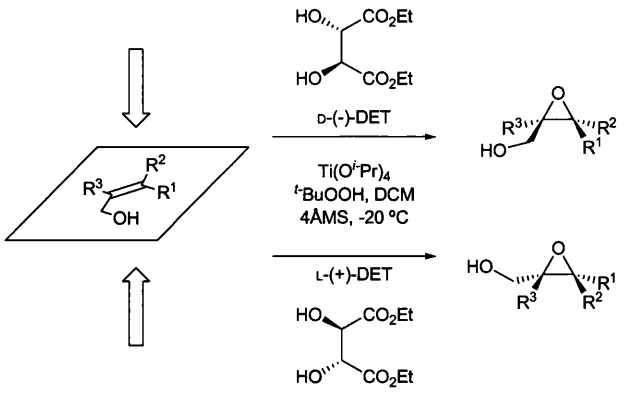



(*S*)-naproxen **54**

97% ee
92% yield

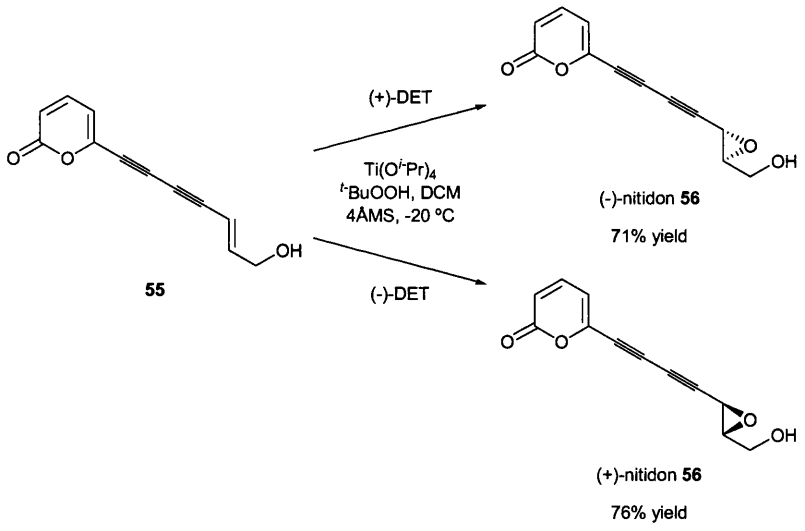
**Scheme 17** *Synthesis of anti-inflammatory agent (S)-naproxen* ***54*** *catalysed by Ru(II)-BINAP complex (S)-****53***

Contemporaneously, Sharpless *et al.* were developing catalysts for asymmetric oxidation reactions. In 1980, the epoxidation of allylic alcohols using titanium *tetra-iso*-propoxide, *tert*-butyl hydroperoxide, and diethyl tartrate (DET) was reported.[23] This process is highly stereospecific and the stereochemical outcome can be easily predicted because the face to be epoxidised is determined by whether (+)- or (-)-diethyl tartrate is used. For example, the use of (-)-diethyl tartrate will direct the epoxidation to the top face of the alkene (as drawn in Scheme 18); whilst (+)-diethyl tartrate will result in the bottom face of the alkene being epoxidised, regardless of the alkene's substitution pattern. This reaction provides an easy and versatile route to synthetically useful epoxy-alcohols, such as (*S*)- and (*R*)-glycidol ($R^1 = R^2 = R^3 = H$) which are useful building blocks for the pharmaceutical industry and are used widely for the synthesis of β-blockers.




**Scheme 18** *Allylic epoxidation catalysed by a Ti-DET complex*

A further example of the use of the Sharpless asymmetric epoxidation is the first total synthesis of naturally occurring (-)-nitidon **56** and its enantiomer (Scheme 19), which have both been found to show remarkable cytotoxic activity against human cancer cell lines *in vitro*.[24] The Sharpless epoxidation provides a versatile and simple route to both enantiomers, through the application the requisite DET enantiomer to achieve the desired stereochemical outcome. Treatment of alkene **55** with (+)-DET under the previous conditions, resulted in (-)-nitidon **56** in 71% yield. It was possible to preliminarily assign the configuration of the epoxide (-)-**56** as (*S,S*), using the paradigm described in Scheme 18.




**Scheme 19** *Sharpless epoxidation in the synthesis of both enantiomers of nitidon* ***56***

Sharpless *et al.* also reported the first catalytic asymmetric dihydroxylation.[25] This used *N*-methylmorpholine *N*-oxide (NMO) **57** (Figure 14) as a stoichiometric oxidant for the osmium tetroxide dihydroxylation. It was also reported that the use of cinchona

alkaloid ligands resulted in an accelerated reaction, meaning that less osmium tetroxide was required. This method was later optimised by the use of $K_2OsO_2(OH)_2$ as the non-volatile source of osmium and dihydroquinine (DHDQ) or dihydroquinidine (DHQD) derived phthalazine (PHAL) ligands (Figure 14), affording the diol products in excellent enantioselectivity ($K_3Fe(CN)_6$ has also been used as the co-oxidant instead of NMO).[26] For example the dihydroxylation of 1,2-diphenylethene **60** with $K_2OsO_2(OH)_2$, $(DHQD)_2PHAL$ **58** and NMO **57** as the stoichiometric oxidant, resulted in diol **61** in 99% ee and 76% yield (Scheme 20).[27] Again the use of ligand dictates the stereochemical outcome of the reaction: if $(DHQ)_2PHAL$ **59** had been used then the diol of the opposite configuration would be obtained.

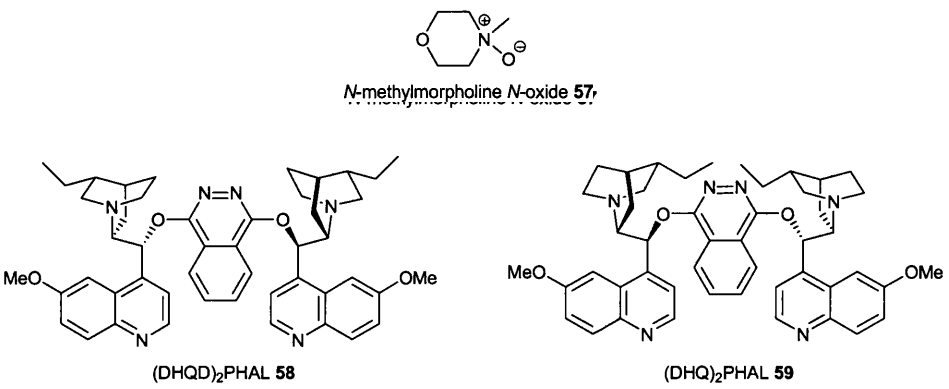
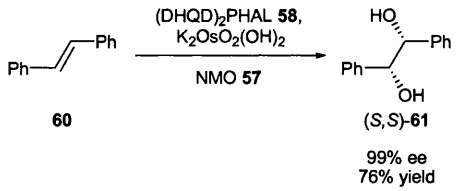
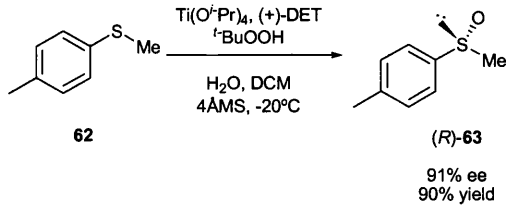



**Figure 14** *NMO **57** and Sharpless dihydroxylation ligands $(DHQD)_2PHAL$ **58** and $(DHQ)_2PHAL$ **59***




**Scheme 20** *Sharpless dihydroxylation of 1,2-diphenylethene **60***

Kagan *et al.* have reported the use of modified Sharpless epoxidation conditions to facilitate the oxidation of a range of sulphides to sulphoxides.[28] It was found that adding one equivalent of water to the standard Sharpless conditions resulted in the sulphoxide products in good enantioselectivity and yield. For example, the treatment of *para*-tolyl methyl sulphide **62** under these conditions resulted in (*R*)-sulphoxide **63** in 91% ee and 90% yield (Scheme 21).




**Scheme 21** *Oxidation of para-tolyl methyl sulphide* ***62*** *using modified Sharpless conditions*

The copper complex of bisoxazoline **64** (Figure 15) has been reported as a catalyst in the cyclopropanation of alkenes (Scheme 22, Table 10).[29] The cyclopropanation products were afforded in high enantio- and diastereoselectivity, which compared favourably to those obtained with other ligands.[30] For example, reaction of styrene **66a** with (-)-menthyl diazoacetate **67** in the presence of copper complex **65** resulted in the cyclopropanation products in a 86:14 diastereoselectivity, with *trans*-**68** in 98% ee and *cis*-**68** in 96% ee (Table 10, entry 1).

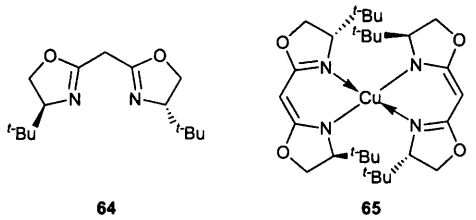
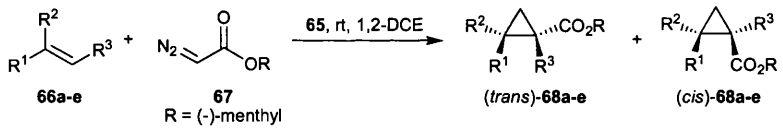



**Figure 15** *Bisoxazoline ligand* ***64*** *and its copper complex* ***65***



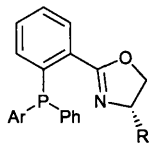

**Scheme 22** *Cyclopropanation of alkenes* ***66a-e*** *catalysed by bisoxazoline copper complex* ***65***

**Table 10**

| Entry | Product | $R^1$ | $R^2$ | $R^3$ | Yield /% | *trans : cis* | ee of *trans-68* /% | ee of *cis-68* /% |
|---|---|---|---|---|---|---|---|---|
| 1 | **68a** | Ph | H | H | 72 | 86 : 14 | 98 | 96 |
| 2 | **68b** | Ph | Me | H | 78 | 89 :11 | 92 | 79 |
| 3 | **68c** | $(CH_2)_5CH_3$ | H | H | 76 | 94 : 6 | 99 | 30 |
| 4 | **68d** | 4-MeO($C_6H_4$) | H | Me | 45 | 98 : 2 | 90 | - |
| 5 | **68e** | $^t$Bu | Me | H | 60 | 95 : 5 | 80 | 91 |

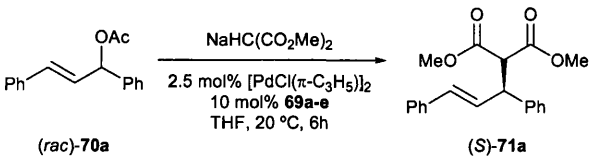
In 1993, Williams *et al.* reported the use of phosphorus containing oxazoline ligands **69a-e** (Figure 16) in the asymmetric palladium catalysed allylic substitution of (*E*)-1,3-diphenylallyl acetate (*rac*)-**70a** (Scheme 23, Table 11).[31] The diester (*S*)-**71a** was

afforded in high enantiomeric excess (90-94%) and yields (88-99%). The best results were obtained using ligand (*S*)-**69c**, which produced the diester in 94% ee and 92% yield (Table 11, entry 3).



(*S*)-**69a**: R = Me, Ar = Ph
(*S*)-**69b**: R = $CH_2Ph$, Ar = Ph
(*S*)-**69c**: R = $^{i}Pr$, Ar = Ph
(*S*)-**69d**: R = Ph, Ar = Ph
(*S*)-**69e**: R = $^{t}Bu$, Ar = Ph
(*S*)-**69f**: R = $^{i}Pr$, Ar = 1-naphthyl

**Figure 16** *Phosphorus containing oxazoline ligands* ***69a-f***



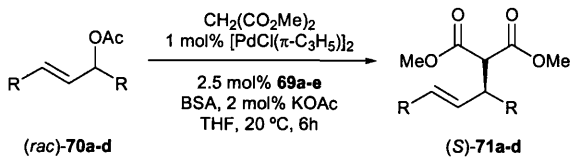

(*rac*)-**70a** (*S*)-**71a**

**Scheme 23** *Palladium catalysed allylic substitution of (rac)-**70a***

**Table 11**

| Entry | Ligand | Yield /% | ee /% |
|---|---|---|---|
| 1 | **69a** | 88 | 90 |
| 2 | **69b** | 96 | 92 |
| 3 | **69c** | 92 | 94 |
| 4 | **69d** | 96 | 92 |
| 5 | **69e** | 99 | 90 |

In the same year both Pfaltz *et al.*,[32] and Helmchen *et al.*[33] also independently reported the use of this type of ligand. Pfaltz *et al.* reported the application of the same group of ligands (**69a-e**) in the allylic substitution of (*E*)-1,3-di-substituted allyl acetates (*rac*)-**70a-d**, resulting in the diester with moderate to excellent enantioselectivities (49-99% ee) and yields (51-99%) (Scheme 24, Table 12). For example, reaction of (*E*)-1,3-diphenyl allyl acetate **70a** with dimethyl malonate in the presence of ligand **69d**, afforded the diester in an excellent 99% ee and 99% yield (Table 12, entry 4).




(*rac*)-**70a-d** (*S*)-**71a-d**

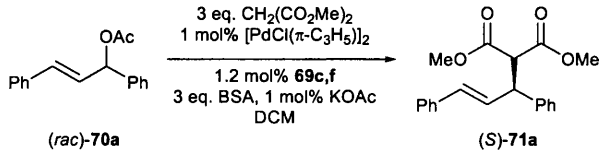
**Scheme 24** *Palladium catalysed allylic substitution of (rac)-**70a-d***

**Table 12**

| Entry | Ligand | 71a (R = Ph) | | 71b (R = Me) | | 71c (R = $^{n}$Pr) | | 71d (R = $^{i}$Pr)[a] | |
|---|---|---|---|---|---|---|---|---|---|
| | | Yield /% | ee /% | Yield /% | ee /% | Yield /% | ee /% | Yield /% | ee /% |
| 1 | **69a** | 98 | 89 | 95 | 56 | 61 | 53 | 91 | 93 |
| 2 | **69b** | 97 | 97 | 75 | 54 | 71 | 63 | 92 | 92 |
| 3 | **69c** | 98 | 98 | 99 | 59 | 72 | 56 | 88 | 94 |
| 4 | **69d** | 99 | 99 | 97 | 50 | 51 | 49 | 93 | 89 |
| 5 | **69e** | 94 | 95 | 96 | 71 | 96 | 69 | 88 | 96 |

[a] $NaCH(CO_2Me)_2$ was used as the nucleophile

Helmchen *et al.* reported the application of ligands **69c** and **69f** in the standard allylic substitution of (*E*)-1,3-diphenyl allyl acetate (*rac*)-**70** with dimethyl malonate (Scheme 25, Table 13).[33] In the presence of ligand **69c** the diester (*S*)-**71a** was obtained in an excellent 98% ee and 96% yield; the use of ligand **69f** with a naphthyl group on the phosphorus required a much longer reaction time in the presence of a higher amount of catalyst and resulted in (*S*)-**71a** in only 78% ee (Table 13, entry 2).




(*rac*)-**70a** (*S*)-**71a**

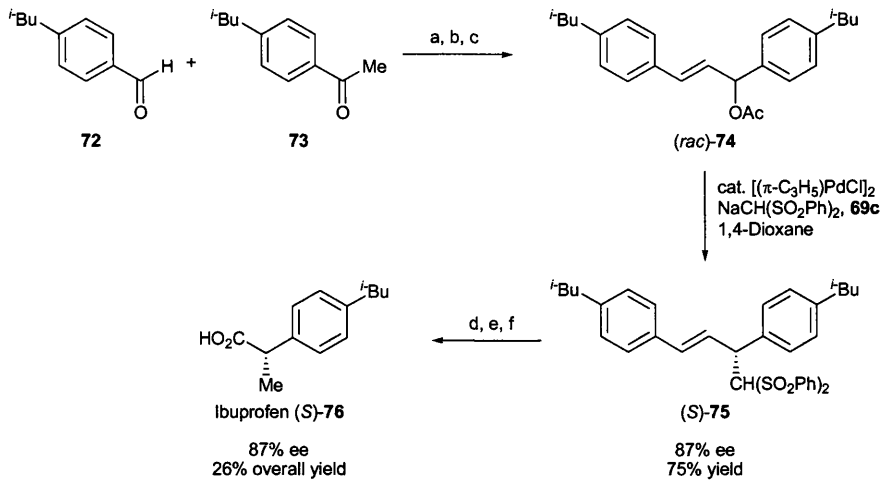
**Scheme 25** *Palladium catalysed allylic substitution of (rac)-**70a***

**Table 13**

| Entry | Ligand | Time /h | Yield /% | ee /% |
|---|---|---|---|---|
| 1 | **69c** | 2 | 96 | 98 |
| 2 | **69f**[a] | 21 | 98 | 78 |

[a] 2 mol% of catalyst

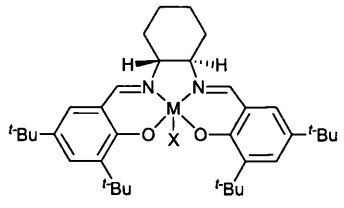
Williams *et al.* have applied ligand **69c** in a key step in the enantioselective synthesis of the anti-inflammatory analgesic, Ibuprofen (*S*)-**76** (Scheme 26).[34] The synthesis involved the formation of acetate (*rac*)-**74** from 4-*iso*-butylbenzaldehyde **72** and 1-(4-isobutylphenyl) ethanone **73**, and its subsequent allylic substitution with sodio*bis*(phenylsulphonyl) methane in the presence of **69c** and $[PdCl(\pi\text{-}C_3H_5)]_2$, to afford the intermediate (*S*)-**75** in 87% ee and 78% ee, which was then transformed into Ibuprofen (*S*)-**76** over three steps. Ibuprofen (*S*)-**76** was obtained in 87% ee and an overall yield of 26%.




a) cat. NaOH(s), EtOH, rt, 12 h, 60%; b) $NaBH_4CeCl_3{\cdot}7H_2O$, MeOH, -10 °C, 1 h, 95%; c) $Et_3N$, $Ac_2O$, cat. DMAP, DCM, rt, 2 h, 95%; d) $O_3$, DCM, MeOH, $NaBH_4$, -78 °C, 4 h. 83%; e) Mg, MeOH, rt-50 °C, 5 h, 89%; f) PDC, DMF, rt, 12 h, 88%

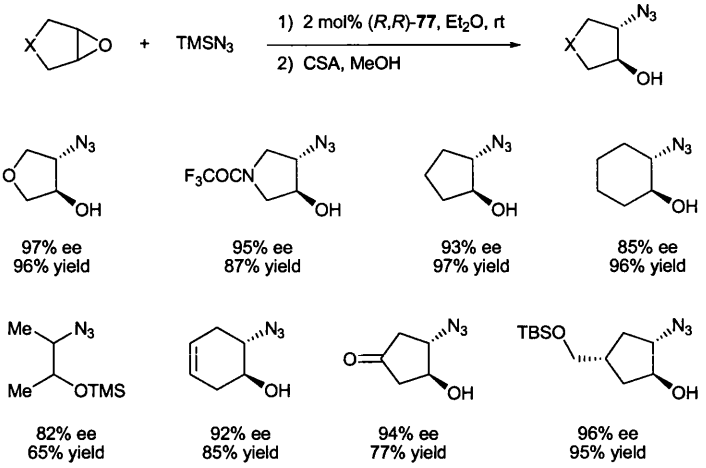
**Scheme 26** *Synthesis of Ibuprofen (S)-**76***

In 1995 Jacobsen *et al.* first reported the development of (salen)chromium and cobalt complexes (Figure 17) which were efficient catalysts for the asymmetric ring-opening of *meso*-epoxides to afford the resulting alcohols in high enantioselectivities and yields.[35] This work was summarised in a review by Jacobsen in 2000 and some examples of the products afforded by this strategy are depicted in Scheme 27.[36] For example, treatment of cyclopentene oxide with trimethylsilyl azide in the presence of 2 mol% of complex (*R*,*R*)-**77** resulted in (1*S*,2*S*)-2-azidocyclopentanol in 93% ee and 97% yield. It was found that the catalyst was sensitive to the size of the substrate and consequently (1*S*,2*S*)-2-azidocyclohexenol was obtained with a lower ee than those products containing a five-membered ring (85% ee, 96% yield).



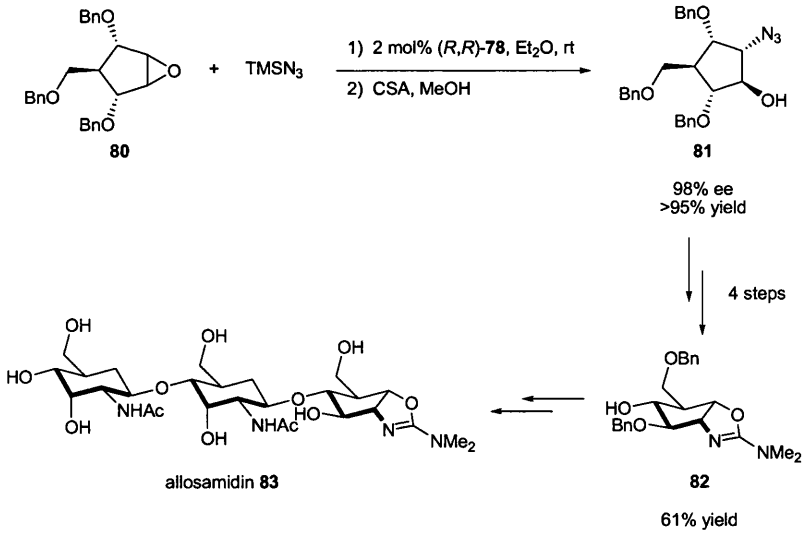

(*R*,*R*)-**77**: M-X = Cr(Cl)
(*R*,*R*)-**78**: M-X = $Cr(N_3)$
(*R*,*R*)-**79**: M-X = Co(OAc)

**Figure 17** *Salen complexes **77-79***




**Scheme 27** *Asymmetric ring-opening of meso-epoxides catalysed by (R,R)-**77***

This method has been applied to the synthesis of a key intermediate in the asymmetric synthesis of the natural product (-)-allsoamidin **83**, which is a potential insecticide or fungicide.[37] Ring-opening of the highly substituted *meso*-epoxide **80** with trimethylsilyl azide in the presence of complex (*R*,*R*)-**78** resulted in the azido alcohol **81** in 98% ee and >95% yield (Scheme 28). This was then further elaborated to yield the key intermediate **82** in 61% yield over 4 steps, which can then be transformed into the target *pseudo*-trisaccharide compound allosamidin **83**.




**Scheme 28** *Application of the asymmetric ring-opening in the synthesis of the key intermediate **82** towards allosamidin **83***

Asymmetric ring opening has also been applied to the kinetic resolution of racemic *meso*-epoxides on both a laboratory and industrial scale.[4,38] Hydrolytic kinetic resolution (HKR), using water as a nucleophile, is effective for the resolution of a wide

range of terminal epoxides, often affording both the epoxide and the corresponding 1,2-diol in very high enantiomeric excess. With few exceptions recovered chiral epoxides can be obtained in >99% ee in up to 46% yield using 0.55 equivalents of water as nucleophile; for example HKR of propylene oxide gave the (*R*)-epoxide in >99% ee and in 46% yield (maximum - 50%) after 18 hours, using only 0.2mol% of catalyst (*R,R*)-**79**.[38] Thus, this methodology has been applied to the kinetic resolution of a wide range of halo-, aryl-, vinyl- and alkynyl- terminal epoxides,[38] and has recently been extended to epoxides containing ω-sulphone,[39] and ω-phosphonate[40] functionalities, all of which afforded chiral epoxides or diols in ≥93% ee (Figure 18).

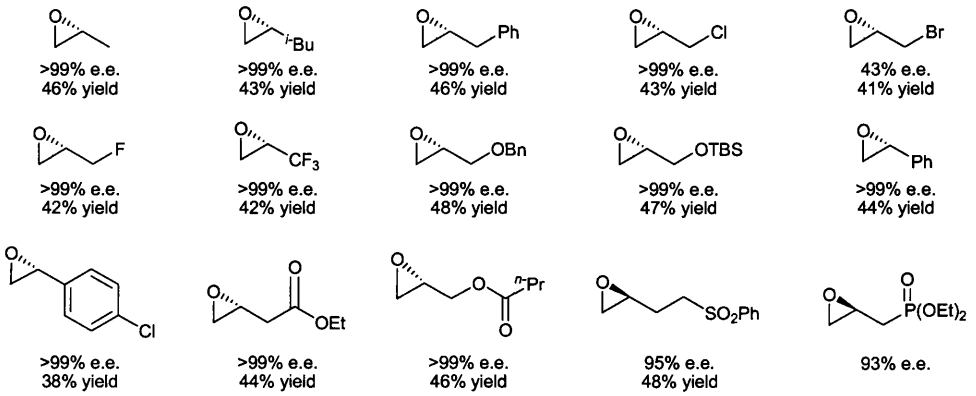



**Figure 18** *A representative range of (rac)-epoxides resolved using HKR*

Unsurprisingly, the generality and broad substrate specificity of HKR has been exploited for the production of a wide range of chiral synthons for natural product synthesis, including recent strategies directed towards the synthesis of Epothilone A,[41] Laulimalide,[42] Fostriecin,[43] arachadonic acid metabolites,[44] bryostatins,[45] ulapualide,[46] α,α-difluoroalkylphosphonate analogues of Lysophosphatidic acid[47] and bicyclic lactones from parasitic wasps,[48] as well as for the enantioselective synthesis of a chiral pyrrolidin-2-one for the treatment of hypertension and arrhythmia.[49] The range of chiral epoxides resolved in these natural product syntheses (Figure 19) stands as true testament to the power of these salen catalysts as routine reagents for asymmetric synthesis.

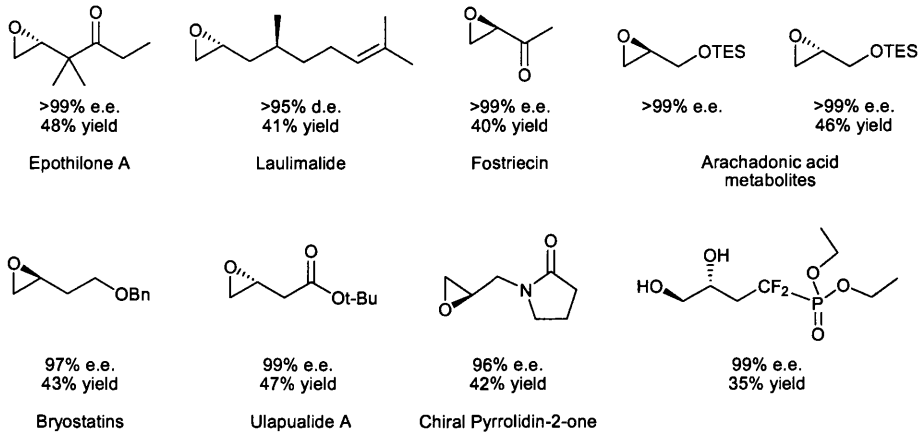



**Figure 19** *Products resolved via HKR in natural product synthesis*

In 1991, Seebach *et al.* reported the development of ligand (*R*,*R*)-**84**, derived from tartrate acetals and aryl Grignard reagents (Figure 20).[50] Spirotitanate (*R*,*R*)-**85** was described as an efficient catalyst for the enantioselective addition of diethyl zinc to aldehydes, resulting in the chiral alcohols in excellent enantioselectivity. For example, treatment of 4-methoxybenzaldehyde **87** with two equivalents of (*R*,*R*)-**85** resulted in alcohol (*R*)-**88** in 98% ee (Scheme 29). However, it was found that that if the concentration of **85** was 0.1 equivalents and an additional 1.2 equivalents of titanium tetra-*iso*-propoxide was added, the selectivity of the addition reaction was reversed, resulting in (*S*)-1-(4-methoxyphenyl)propan-1-ol **88** in 94% ee (Scheme 29).

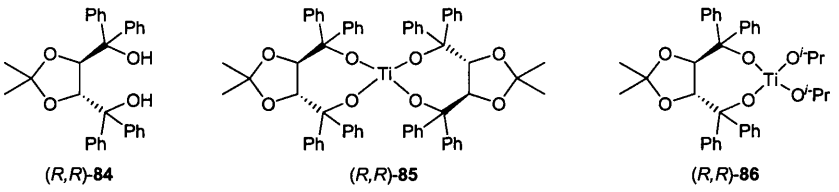
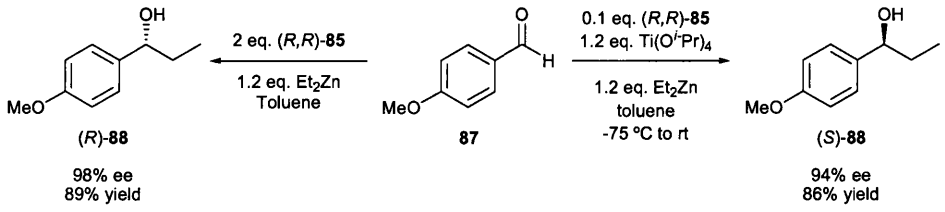



**Figure 20** *TADDOL ligands **84** and their spirotitanate and bicyclic titanate complexes **85** and **86** respectively*




**Scheme 29** *Diethyl zinc addition to 4-methoxybenzaldehyde **87** catalysed by spirotitanate **85***

It was later reported that treatment of the spirotitanate (*R*,*R*)-**85** with one equivalent of titanium tetra-*iso*-propoxide resulted in the bicyclic titanate (*R*,*R*)-**86**, which was found

to be a more effective catalyst than the spirotitanate.[51] For example, treatment of 4-methoxybenzaldehyde **87** with (*R*,*R*)-**86** under the standard catalytic conditions at -25 °C (1.2 eq. Ti(O$^i$Pr)$_2$, 1.2 eq. $Et_2Zn$) resulted in (*S*)-1-(4-methoxyphenyl)propan-1-ol **88** in 96% ee. This approach has been applied to aldehyde substrates with various functionalities; examples of products obtained using this approach are depicted in Figure 21.

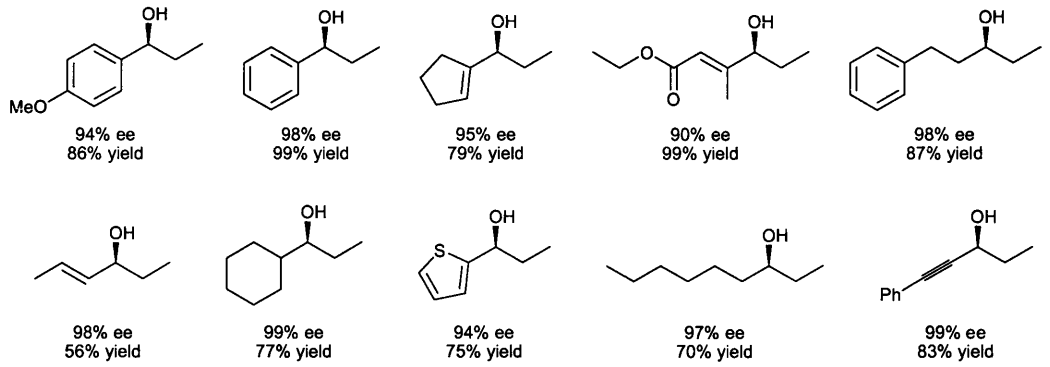



**Figure 21** *Products of the (R,R)-**86** catalysed addition of diethyl zinc to aldehydes*

The (*R*,*R*)-**86** catalysed diethyl zinc addition to aldehydes was also found to be diastereoselective when applied to chiral aldehydes (Figure 22). The nature of the addition is dictated by the chirality of the ligand and not the stereogenic centre in the substrate.

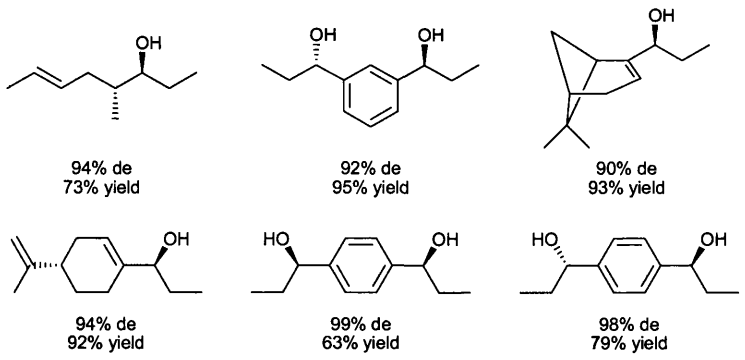



**Figure 22** *Products of the diastereoselective (R,R)-**86** catalysed addition of diethyl zinc to aldehydes*

Addition reactions with other nucleophiles have also been demonstrated using R-Ti(O$^i$Pr)$_3$ derivatives generated *in situ* from the corresponding Grignard or lithium reagents in conjunction with titanate complex (*R*,*R*)-**86**.[52] Examples are shown in Figure 23, with the introduced groups highlighted in blue.

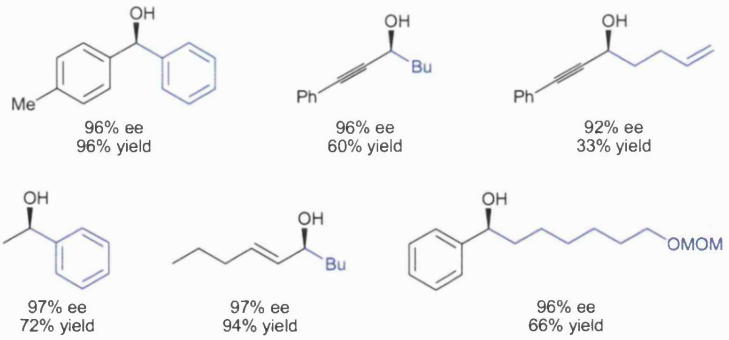



**Figure 23** *Secondary alcohols from the nucleophilic addition to aldehydes. The groups in blue are those introduced with R-Ti(O$^i$Pr)$_3$ by addition to the corresponding aldehyde*

Due to the generality of this procedure TADDOLates are consistently used as a benchmark against which potential ligands are measured.

## 1.2 $C_3$-Symmetric Ligands

The high level of stereocontrol achieved with $C_2$-symmetric ligands has led to many ligands being developed with this symmetry characteristic.[53] However, the potential of chiral ligands with higher rotational symmetry to induce much higher enantioselectivities has been less well explored.[54,55] To explain the potential of chiral $C_3$-symmetric ligands for asymmetric catalysis, it is necessary to consider the effects of ligand symmetry on square planar and octahedral complexes (Figure 24).[55]

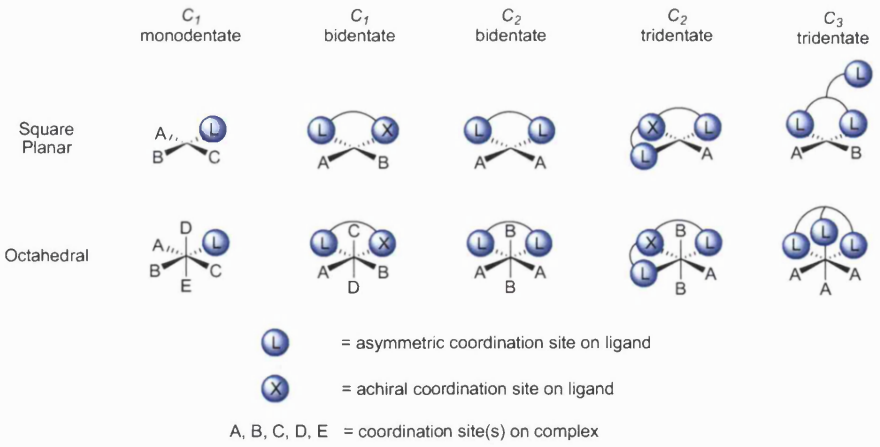
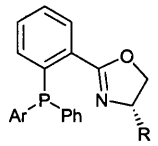



**Figure 24** *Symmetry and geometry in square planar and octahedral complexes*

The simplest system is one containing a monodentate $C_1$-symmetric ligand, in which all of the vacant coordination sites are different, regardless of the complex's geometry. Consequently, the enantioselectivity induced by this type of ligand is normally poor. However, the use of a $C_1$-symmetric bidentate ligand with two different coordinating

atoms with only one having a chiral environment, often results in high enantioselectivity. An example is the family of ligands **69a-f** which was reported independently by Williams *et al.*,[31] Pfaltz *et al.*,[32] and Helmchen *et al.*[33] (Figure 25). As seen previously, these ligands have proved very efficient in the asymmetric palladium catalysed allylic substitution (section 1.1.4). This is due to the bidentate nature of the ligand, which decreases the number of available coordination sites, thus resulting in a higher enantioselectivity.




(*S*)-**69a**: R = Me, Ar = Ph
(*S*)-**69b**: R = $CH_2Ph$, Ar = Ph
(*S*)-**69c**: R = $^{i}Pr$, Ar = Ph
(*S*)-**69d**: R = Ph, Ar = Ph
(*S*)-**69e**: R = $^{t}Bu$, Ar = Ph
(*S*)-**69f**: R = $^{i}Pr$, Ar = 1-naphthyl

**Figure 25** *Phosphorus containing oxazoline ligands* ***69a-f***

In the case of bidentate $C_2$-symmetric ligands, the remaining coordination sites (A) in a square planar complex are equivalent, meaning that binding of the prochiral substrate affords identical metal-substrate complexes, thus increasing the enantioselectivity. In an octahedral complex however, a $C_2$-symmetric ligand affords a complex with two different possible coordination sites (A and B), which may result in lowering of the selectivity induced by the ligand. A tridentate $C_2$-symmetric ligand in a square planar complex will result in only one available coordination site, whilst in an octahedral complex it will afford two different vacant sites (A and B) in a 2:1 ratio, thus potentially reducing the stereocontrol. Finally, a $C_3$-symmetric ligand in a square planar complex, results in two different coordination sites, though proves superior to the $C_2$-symmetric ligands in an octahedral environment where all three vacant sites are equivalent. Thus, for catalytic reactions that proceed through octahedral metal-ligand-substrate complexes, the use of $C_3$-symmetric ligands has the potential to enhance stereocontrol. This is obviously not the case for a square planar complex as the coordination of a $C_3$-symmetric ligand causes the two remaining sites to be different.

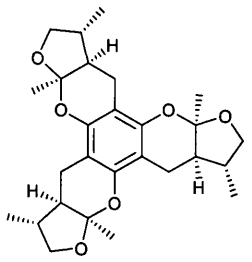
An alternative detrimental scenario must also be considered since the $C_3$-symmetric ligand may deactivate the catalyst by creating a metal centre which is too electron rich to be catalytically active, due to the three donating sites of the ligand. Nonetheless, a

number of reports have been published on $C_3$-symmetric molecules and their use for the preparation of chiral metal and their applications are now reviewed herein.

## 1.3 $C_3$-Symmetry in Nature

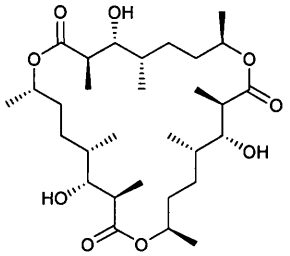
Chemists are not the first to discover the potential of $C_3$-symmetrical molecules as structural elements; nature has been using them for millennia. $C_3$-Symmetrical natural products have been isolated from marine organisms, algae and fungi, which exhibit various biological activities, such as antibacterial and antiviral.[56] Some of the products that have been isolated are depicted in Figure 26.

a[57]



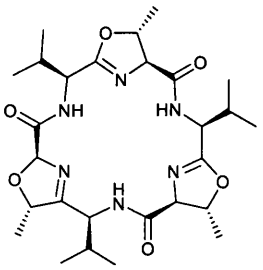
Xyloketal from Mangrove Fungus Xylaria sp. from the South China Sea Coast

b[58]



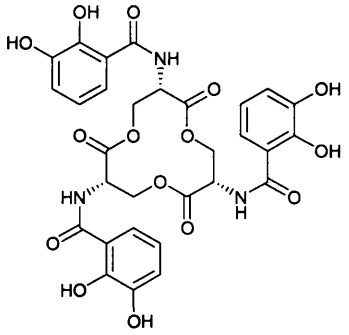
Dasypogalactone, a macrolactone from the Indonesian Lichen Usnea Dasypoga

c[59]



Westiellamide, a Lissoclinum cyclopeptide alkaloid

d[60]



Enterobactin from escherichia-coli: a siderophore playing an important role in bacterial iron uptake

**Figure 26** *$C_3$-Symmetric natural products*

## 1.4 $C_3$-Symmetry in Chemistry

### 1.4.1 $C_3$-Symmetric Complexes and Molecules

$C_3$-Symmetric complexes and molecules have been embraced by the inorganic community as objects of structural interest and beauty. Many $C_3$-symmetric complexes incorporating metals that are known to catalyse organic transformations have been reported, yet very few have been screened for catalytic activity. A representative array of these types of complexes is shown in Figure 27.

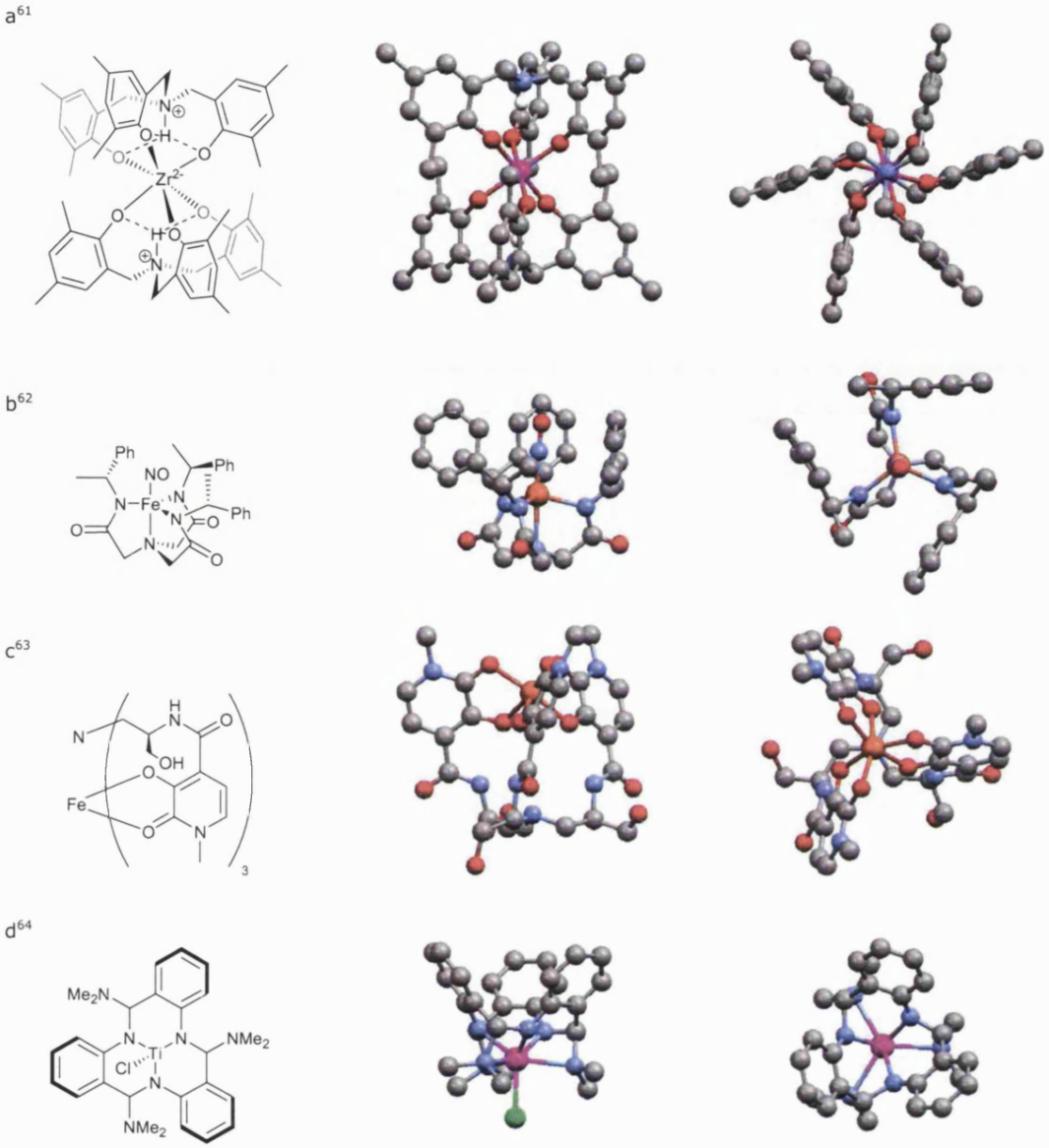
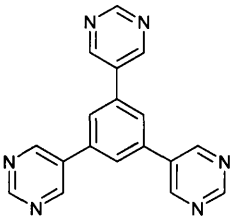
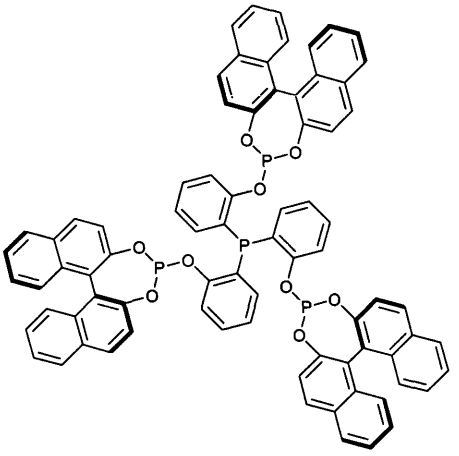
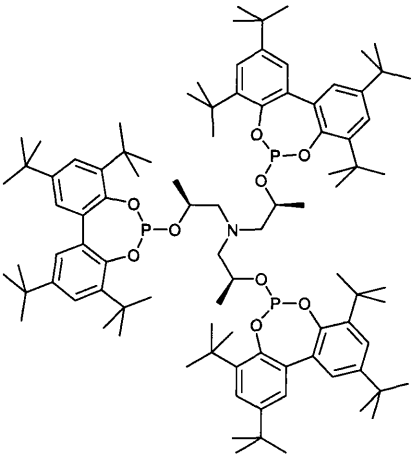
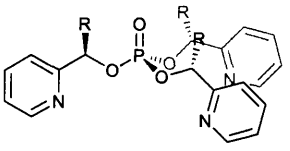
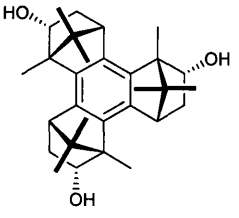


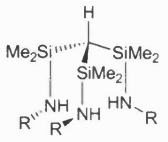

**Figure 27** *Representative examples of previously reported $C_3$-symmetric complexes, showing the structure and side-on and top views of the X-ray structure (where applicable)*

Several other $C_3$-symmetric molecules have been reported, but not all have been applied as ligands or receptors. A few of these are reported to have been complexed to metals, but structural and crystal data has not been presented and neither has any catalytic activity. These will not be covered in this review, but a representative array of these molecules is depicted in Table 14.

**Table 14**

| Entry | Molecule | Metal Complex Reported |
|---|---|---|
| a[65] |  | Pd |
| b[66] |  | Pt |
| c[67] |  | Rh |
| d[68] |  R = Me, R = $^{t}$Bu<br>R = neomenthyl | - |
| e[69] |  | - |

Certain molecules have been reported as ligands for several different metals. These complexes have been shown to exhibit different properties, with only some showing catalytic activity. For example ligands of the type **89** have been shown to complex to zirconium, titanium, and lithium to afford $C_3$-symmetric complexes (Figure 29), but only the zirconium complex has been reported as a catalyst (*vide infra*).[70,71] Interestingly, the same type of ligand can exhibit different architecture in complexes, depending on the metal centre that is incorporated; for example, the complexes of ligand **89a** and **89b** with zirconium and titanium contain only one metal centre, whereas the lithium complex of **89b** contains three.




**89a**: R = (*R*)-1-indanyl
**89b**: R = (*S*)-1-CH(CH$_3$)Ph

**Figure 28** *Tripodal amine ligands* ***89a,b***

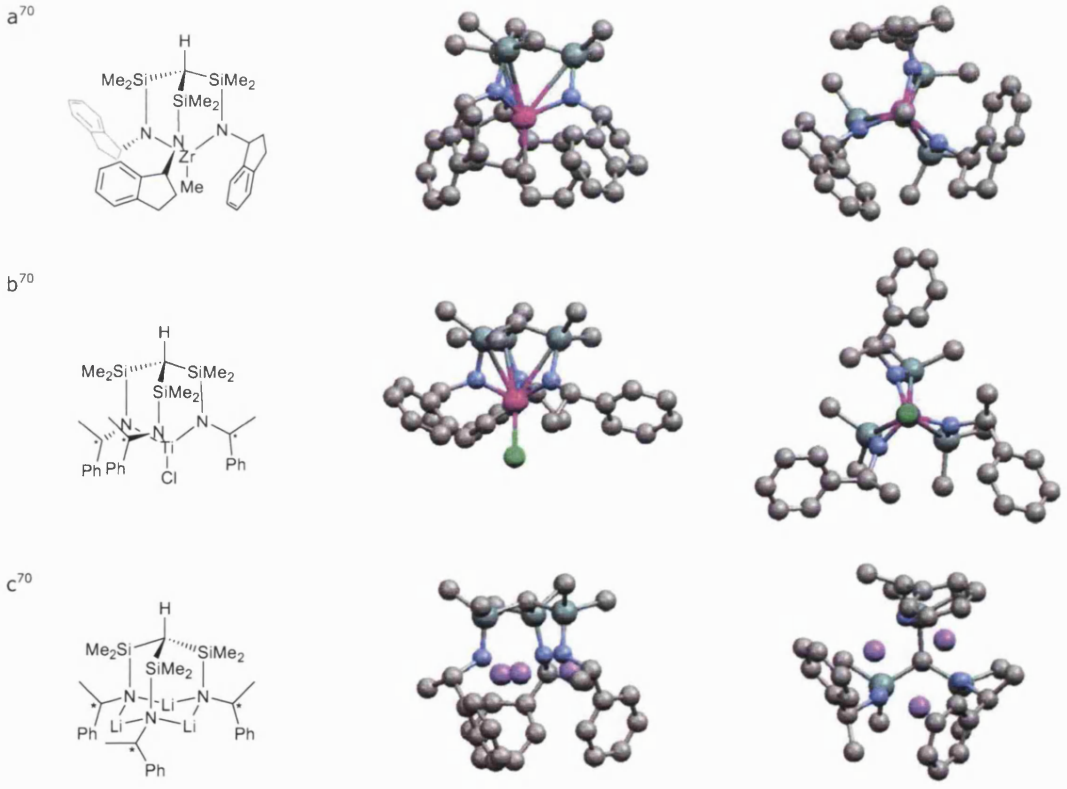
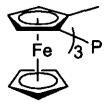


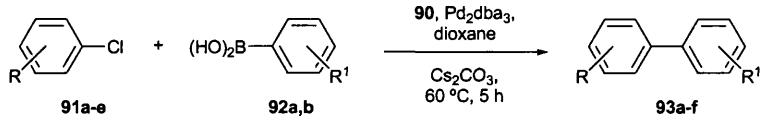

**Figure 29** *Examples of different complexes with the same family of ligands* ***89a,b***

$C_3$-Symmetric ligands and complexes have proved their efficacy for catalysis with their application to achiral transformations. For example, the complex resulting from the treatment of monodentate $C_3$-symmetric tris(2-methyl ferrocenyl)phosphine ligand **90** (Figure 30) with $Pd_2dba_3$, has proven to be a good catalyst for the Suzuki coupling of aryl chlorides and substituted phenylboronic acids under mild conditions (Scheme 30, Table 15).[72] The reaction conditions were optimised for the reaction of *para*-chlorotoluene and phenylboronic acid and then applied to a range of substrates, resulting in the coupled products in good yields (36-90%). Interestingly, although the use of *ortho*-substituents was found to reduce the efficiency of the reaction, moderate conversions were still achieved.




**90**

**Figure 30** *Tris(2-methyl ferrocenyl)phosphine monodentate ligand* ***90***




**91a-e** **92a,b** **93a-f**

**Scheme 30** *Suzuki coupling of aryl chlorides and substituted phenylboronic acids* ***91a-e***

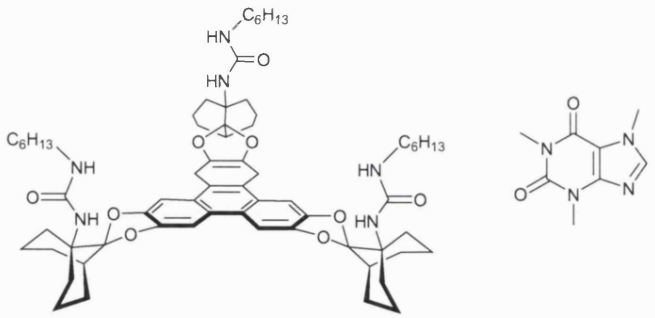
**Table 15**

| Product | R | $R^1$ | Yield /% |
|---|---|---|---|
| **93a** | 4-Me | H | 80 |
| **93b** | 4-$NO_2$ | H | 90 |
| **93c** | H | 2-Me | 57 |
| **93d** | 2-Me | H | 49 |
| **93e** | 2-Me | 2-Me | 46 |
| **93f** | 2-OMe | 2-Me | 36 |

### 1.4.2 $C_3$-Symmetric Receptors

$C_3$-Symmetric molecules have also been investigated as chiral receptors for a variety of guests. Representative examples of recent applications of these types of receptors are briefly reviewed herein.

Novel $C_3$-symmetric artificial receptors for caffeine **95** and other alkylated oxopurines, based on a trifunctionalised triphenylene ketal scaffold such as **94** have been reported (Figure 31).[73]



94 95

**Figure 31** *$C_3$-Symmetric artificial receptor **94** for caffeine **95***

It was found that rigid receptor **94** had a much higher caffeine binding constant than its flexible analogues. A crystal structure of the complex of **94** with caffeine **95** was obtained indicating that the three distal urea protons from the phenanthrene unit, form hydrogen bonds to the caffeine guest.

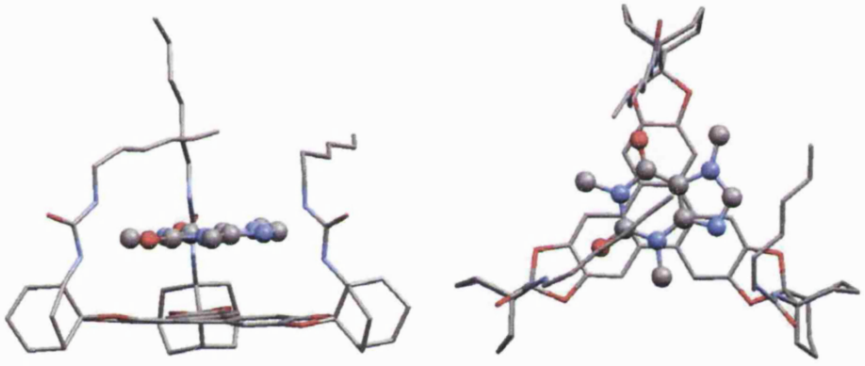


**Figure 32** *Side on and top views (left and right respectively) of the X-ray crystal structure of the complex of **94** with caffeine **95**. Caffeine illustrated as ball and stick for clarity.*

In 2001, H-J. Kim *et al.* reported the use of benzene based $C_3$-symmetric chiral tris(oxazoline) derivative **96a** (Figure 33) as hosts for sugar recognition, one of the more challenging aspects of supramolecular chemistry.[74] The three oxazoline nitrogens act as H-bonding acceptors for the polar hydroxyl groups of the carbohydrate, and a central phenyl group acts as a π-donor for C-H-π interactions.

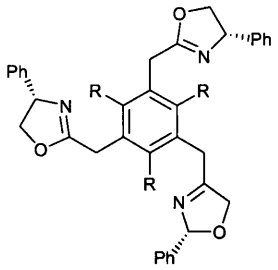
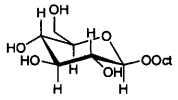
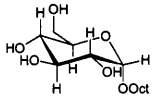
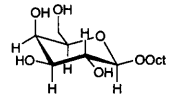
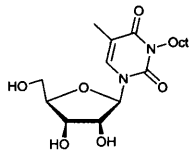



**Figure 33** *Benzene based $C_3$-symmetric chiral tris(oxazoline) derivatives* ***96a,b***

When the receptors were screened with a variety of sugars and alcohols in chloroform, it was found that both gave very similar binding constants for each guest, indicating that the chirality of the host had little effect on the stereoselective discrimination of different types of sugar. The binding constant between (*S*)-**96a** and *n*-octyl-β-D-glucopyranoside was over 4 times greater than for its α-anomer and the binding to *n*-octyl-β-D-galactopyranoside was 4 times weaker than that of *n*-octyl-β-D-glucopyranoside. These differences in the binding were postulated to be due to the energetic difference in the hydrogen-bonding patterns due to the varying degree of steric interactions between the sugars and **96a**. It was also found that the binding was dramatically reduced when the receptor interacted with alcohols with fewer hydroxyl groups, indicating that the number of hydrogen-bonds formed is important in these molecular recognition systems.

**Table 16**

| Guest Structure | Name | $K_a$ /M$^{-1}$ | |
|---|---|---|---|
| | | (*S*)-96a | (*R*)-96a |
|  | Octyl β-D-Glucoside | 1120(±42) | 1190(±120) |
|  | Octyl α-D-Glucoside | 270(±46) | 310(±18) |
|  | Octyl β-D-Galactoside | 250(±20) | 250(±22) |
|  | Uridine | 80(±23) | 62(±25) |
|  | *cis*-1,2-Cyclohexanediol | 40(±13) | |

A year later, S-G. Kim *et al.* reported the enantiomeric recognition of α-chiral primary ammonium ions with the same family of benzene-based tripodal tris(oxazoline) receptors (Figure 33).[75] When different guest salts were screened with host **96b**, it was found that good levels of selectivity could only be obtained for α-aryl-substituted guest molecules; where π-π interactions between the guest and host play a significant role in the selectivity by stabilising the inclusion complexes (Table 17).

**Table 17**

| Racemic Ammonium Guest | Enantioselectivity[a] | Extraction /%[b] |
|---|---|---|
| α-phenylethylamine | 71 (*R*) : 29 (*S*) | 82 |
| α-(1-naphthyl) ethylamine | 70 : 30 | 99 |
| phenylglycine methyl ester | 78 (*S*) : 22 (*R*) | 60 |
| tryptophan methyl ester | 67 (*S*) : 33 (*R*) | 57[c] |
| alanine methyl ester | 53 (*S*) : 47 (*R*) | 41 |
| phenylalanine methyl ester | 55 (*S*) : 45 (*R*) | 36 |

[a]Enantioselectivity of ammonium ion extracted from excess racemic salts ($RNH_3^+Cl^-$, 10 M equiv., 0.5 M $D_2O$; 0.6 M $NaPF_6$) by **96b**; (0.05 M in $CDCl_3$) at 25 °C. [b]Percentage of ammonium salts extracted into $CDCl_3$ with respect to **96b**. [c]Extraction at 45 °C.

The X-ray crystal structure confirmed that the receptor binds the ammonium ion in a $C_3$-symmetric environment, bonding to the ion *via* hydrogen bonds to the oxazoline nitrogen atoms (Figure 34). This also confirms the π-stacking between the phenyl rings of the guest and receptor.

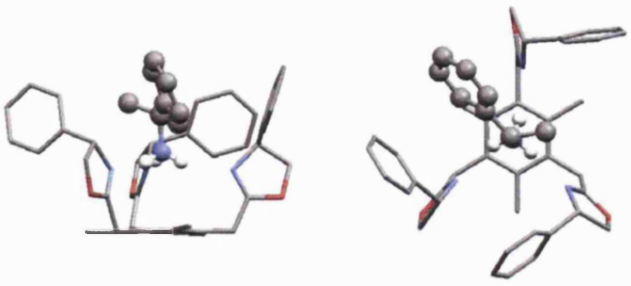
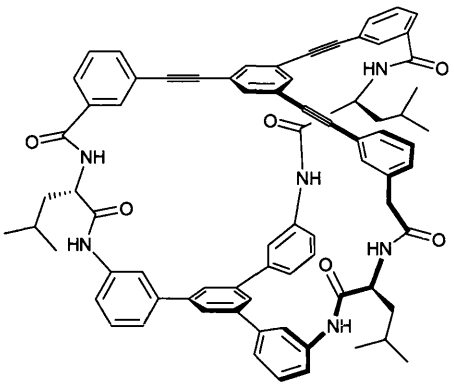


**Figure 34** *Side and top views (left and right respectively) of the X-ray crystal structure of inclusion complex* ***96b****-(R)-phenylethylamine. (Hydrogen atoms are omitted for clarity, except for the three $NH_3^+$ hydrogen atoms)*

In 2003, Diederich *et al.* reported the development of $C_3$-symmetric receptors incorporating 1,3,5-triphenyl benzene and 1,3,5-tris(phenylethynyl)benzene units to create an inclusion cavity.[76] The binding constants of these receptors with octyl D-glucosides were moderate, with the best results being with receptor **97** (Figure 35) and octyl β-D-glucoside ($K_a$ = 270 $M^{-1}$ at 300K). It was proposed that in these complexes,

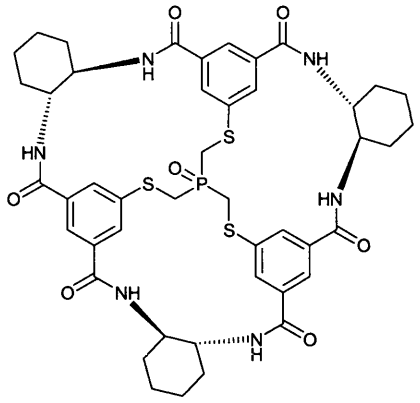
the glucosides were bonding to one of the external faces of the receptors rather than within the cavity.




**97**

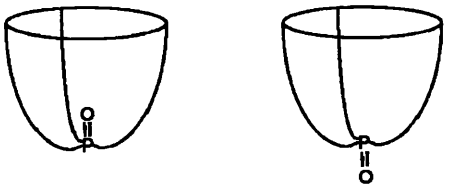
**Figure 35** *$C_3$-Symmetric receptor **97***

Hong *et al.* reported the development of a bowl-shaped $C_3$-symmetric receptor **98** (Figure 36) with a phosphine oxide functionality within the cavity to act as a H-bond acceptor.[77] This combined with the donor and acceptor groups on the periphery were proposed to enhance the enantioselectivity in the binding of amino acid derivatives. Receptor **98** was produced as a ~10:1 (**98a**:**98b**) inseparable mixture of conformational stereoisomers caused by the phosphine oxide moiety being directed either inside or outside of the cavity (Figure 37). Analysis of the $^{31}P$ NMR spectrum of the complex of **98** with bulky Lewis acid $Ph_2SnCl_2$ revealed a downfield shift for the $^{31}P$ resonance of the minor isomer. This implies that the minor isomer has its phosphine oxide directed outside of the cavity because this bulky Lewis acid is less likely to form a 1:1 complex when the phosphine oxide moiety is directed inside the cavity. Treatment with $NH_4^+$ displayed a downfield shift for the major product, implying that this isomer has the phosphine oxide moiety directed within the cavity.



98

**Figure 36** *Concave receptor **98***



**98a** **98b**

**Figure 37** *Representations of the two stereoisomers of the concave ligand **98**, with the phosphine moiety being directed into the cavity (**98a**) or out of the cavity (**98b**)*

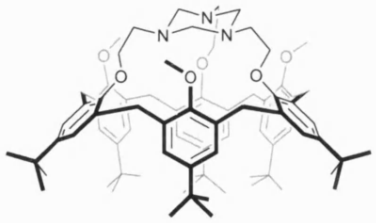
To test the binding capability of receptor **98a**, NMR titration experiments were performed with *N*-dodecylamide amino acid derivatives (Table 18). It was found that derivatives with strongly H-bonding side chains such as aspartic acid (Asp, $CO_2H$), asparagine (Asn, $CONH_2$), glutamic acid (Glu, $CO_2H$) and glutamine (Gln, $NH_2$) exhibited better binding affinity than those with lipophilic side chains. The strongest binding was displayed with D-asparagine, which had a binding constant of 45000 $M^{-1}$, with the receptor preferentially complexing the D-isomer. At the time of publication the authors were unsure of the exact structural origin of this preference, though investigations into the thermodynamics of the complexes revealed that binding of the D-asparagine derivative was enthalpically less favourable, but entropically more favourable compared to the L-isomer. This is indicative of the fact that the structural changes occurring during the process of complexation are less significant when **98a** is binding to D-Asn-NHR than when binding occurs to L-Asn-NHR (R = docecyl). The presence of the phosphine oxide functionality in the interior of the molecular bowl is believed responsible for the high levels of binding, especially for asparagine derivatives, due to participation of the P=O in cooperative H-bonding with the guanidinium functionality of guest.

**Table 18**

| Guest[b] | $K_a$[a] /M$^{-1}$ | | Enantioselectivity |
|---|---|---|---|
| | D | L | |
| D,L-Val-NHR[c] | 400 | 80 | 83 : 17 |
| D,L -Phe-NHR | 1000 | 170 | 85 : 15 |
| D,L -Ser-NHR | 1800 | 1500 | 55 : 45 |
| D,L -Thr-NHR | 2250 | 1050 | 68 : 32 |
| D,L -Asn-NHR | 45000 | 12000 | 79 : 21 |
| D,L -Asn-(β-NHMe)-NHR | 3100 | 2000 | 61 : 39 |
| D,L -Asp-NHR | 5000 | 1600 | 76 : 24 |
| D,L -Gln-NHR | 3000 | 2000 | 60 : 40 |
| D,L -Glu-NHR | 5200 | 700 | 88 : 12 |

[a] Binding constants measured by $^1$H NMR titration in $CDCl_3/CD_3OD$ (10:1 v/v) at 25 °C; [b] Guests were used as the trifluoroacetate salts. [c] R = docecyl.

The novel $C_3$-symmetric calix[6](aza)cryptand **99** (Figure 38) was also reported as an efficient and selective receptor for small ammonium ions (Table 19).[78] The calixcryptand showed the strongest binding with ethylammonium ions (Table 19, entry 3), whilst binding was relatively poor with secondary and tertiary ammonium ions (Table 19, entries 6 and 7), with no binding being observed for quaternary ammonium ions (Table 19, entry 8). A solution of calixcryptand **99** in chloroform was found to extract ammonium ions out of water, indicating its potential as a phase transfer catalyst.



**99**

**Figure 38** *Novel $C_3$-symmetric calyx[6](aza)cryptand* ***99***

**Table 19**

| Entry | Ammonium Picrates | $K_a \times 10^{-4}$ / M$^{-1}$ | Extraction /% |
|---|---|---|---|
| 1 | $NH_4^+Pic^-$ | 21 100 | 68 |
| 2 | $MeNH_3^+Pic$ | 11 600 | 74 |
| 3 | $EtNH_3^+Pic$ | 32 800 | 81 |
| 4 | $PrNH_3^+Pic$ | 5120 | 73 |
| 5 | $BuNH_3^+Pic$ | 124 | - |
| 6 | $Me_2NH_2^+Pic$ | 276 | - |
| 7 | $Me_3NH^+Pic$ | 5.2 | - |
| 8 | $Me_4N^+Pic$ | - | - |

The host-guest complexes were analysed by $^1$H NMR, which revealed that an *endo*-complex was formed in all cases. This was evident by the resonances for the guest molecule being at high chemical shifts. The X-ray crystal structure was obtained for the complex with the propyl ammonium ion, confirming this structure (Figure 39).

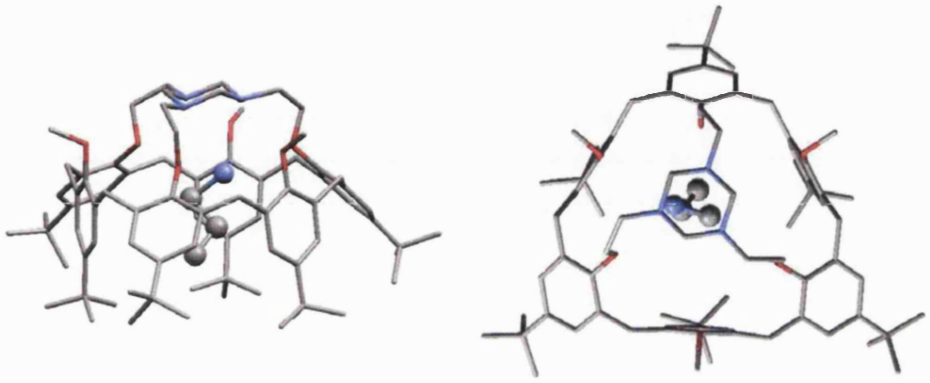


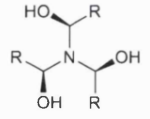
**Figure 39** *Side and top views of X-ray crystal structure of the complex of* ***99*** *with* $PrNH_3^+$ *emphasised as ball and stick and receptor as a wire-frame for clarity*

### 1.4.3 Applications in Catalysis

The applications of a range of $C_3$-symmetric complexes for asymmetric catalysis are reviewed herein, with reactions classified according to the ligand type used for catalysis.

#### Tripodal Hydroxyl Ligands

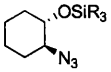
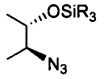
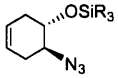
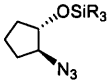
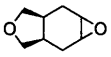
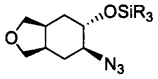
In 1992, Nugent reported the seminal use of $C_3$-symmetric trialkanolamine **100a** as a ligand for asymmetric transformation.[79] The zirconium complex which resulted from the treatment of **100a** with $Zr(O^tBu)_4$ and water, (**100a**-Zr-OH)$_2$·$^t$BuOH **101**, was found to promote the enantioselective ring-opening of *meso*-epoxides with azidosilanes in good yields (59-86%) and enantioselectivities (83-93%). For example, the reaction of cyclohexane oxide and azidosilane in the presence of complex **101** and trimethylsilyl trifluoroacetate gave the ring-opened azide product in 93% ee and 86% yield (Table 20, entry 1).



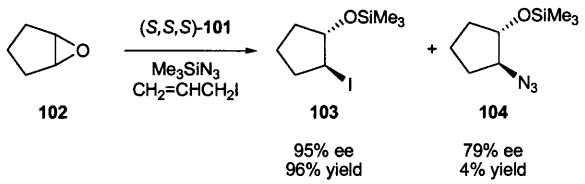

(*S,S,S*)-**100a**: R = Me
(*S,S,S*)-**100b**: R =Ph
(*S,S,S*)-**100c**: R = $^t$Bu

**Figure 40** *$C_3$-Symmetric triol ligands (S,S,S)-**100a-c***

**Table 20**

| Entry | *meso*-Epoxide | Azide | T /°C | Product | Yield /% | ee /% |
|---|---|---|---|---|---|---|
| 1 |  | $^{i}$PrMe$_2$SiN$_3$ | 0 |  | 86 | 93 |
| 2 |  | $^{i}$PrMe$_2$SiN$_3$ | 0 |  | 59 | 87 |
| 3 |  | $^{i}$PrMe$_2$SiN$_3$ | 25 |  | 79 | 89 |
| 4 |  | $^{i}$PrMe$_2$SiN$_3$ | 25 |  | 64 | 83 |
| 5 |  | Me$_3$SiN$_3$ | 25 |  | 78 | 88 |

A mechanistic study was subsequently published in 1998, which revealed that the complex existed as an interconverting mixture of dimeric and tetrameric zirconium tri-*iso*-propanolamine complexes, with the active species being the dimeric form.[80] The involvement of two metal centres results in an azide-zirconium complex in which one metal is complexed to the azide and the other activates the epoxide. The transfer of the azide to the epoxide is the rate-determining step and it was postulated that the azide could be replaced by another nucleophile before this step occurs, resulting in the enantioselective transfer of an alternative nucleophile.[81] In order to test this premise, cyclopentene oxide **102** was treated with azidotrimethylsilane under the same conditions as before, but in the presence of two equivalents of allyl iodide (Scheme 31). The β-iodohydrin **103** was obtained in 95% ee and 96% yield, whilst the competing azide product **104** was only produced in 4% yield, but with an enantioselectivity of 79%.

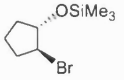
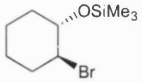
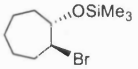
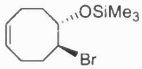
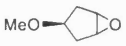
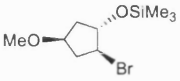



**Scheme 31** *Desymmetrisation of cyclopentene oxide to yield β-iodohydrin **103***

This desymmetrisation of a series of *meso*-epoxides was extended using allyl bromides to afford a series of chiral protected β-bromohydrins (Table 21). It was found that as allyl bromide is a poorer alkylating agent, a large excess of allyl bromide was necessary

to suppress the competing azide formation, with twenty equivalents of allyl bromide being required to maintain the yield of the azide product to below 5%.

**Table 21**

| Epoxide | Product | Yield /% | ee /% |
|---|---|---|---|
|  |  | 81 | 95 |
|  |  | 86 | 91 |
|  |  | 90 | 89 |
|  |  | 92 | 84 |
|  |  | 89 | 96 |

In 1994 Nugent *et al.* demonstrated the use of triol (*S,S,S*)-**100a** and (*S,S,*S)-**100c** as ligands for titanium and vanadium, resulting in monomeric $C_3$-symmetric complexes **105a** and **106c** (Figure 41).[82]

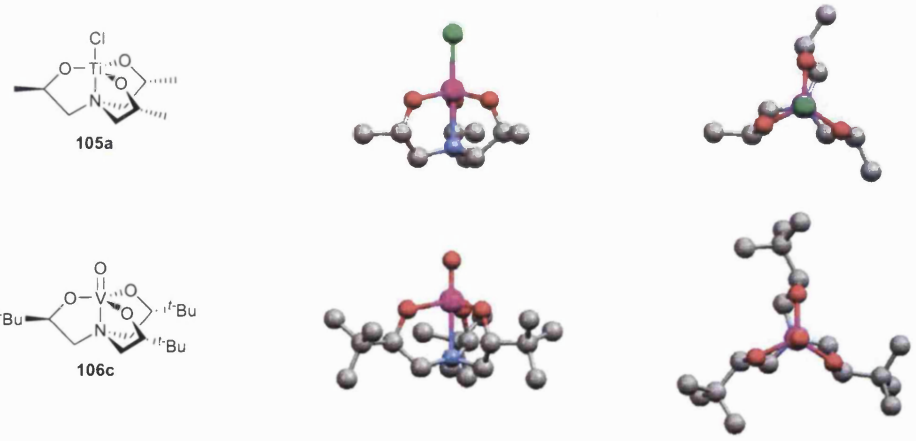
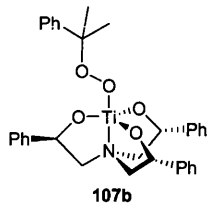



**Figure 41** *Complexes **105a** and **106c** (top and bottom respectively) and side and top views of their X-ray crystal structures (left and right respectively)*

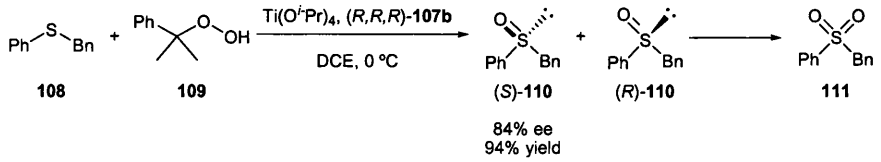
In 1996, the application of ligands **100a-c** to the titanium catalysed oxidations of sulphides was reported.[83] The peroxo-titanium complex **107b** (Figure 42), formed by treatment of (*R,R,R*)-**100b** with titanium *iso*-propoxide followed by cumyl hydroperoxide, was found to have the highest catalytic activity of the three complexes. The investigated procedure was optimised for the oxidation of *para*-tolyl methyl

sulphide and then extended to a range of other aryl sulphides resulting in (*S*)-sulphoxide products being formed in moderate to good enantioselectivities. The best results were obtained for the oxidation of phenyl benzyl sulphide with cumyl hydroperoxide **109** using 0.01% catalyst **107b** (with respect to the oxidant) to afford (*S*)-sulphoxide **110** in 84% ee and 94% yield (Scheme 32). The over-oxidised sulphone product **111** was also observed in a 77:23 (**110**:**111**) ratio.




**107b**

**Figure 42** *Peroxotitanium complex* ***107***




**108** **109** (*S*)-**110** (*R*)-**110** **111**

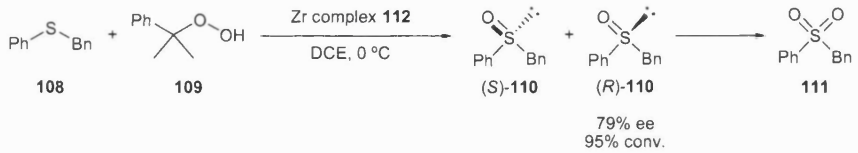
84% ee
94% yield

**Scheme 32** *Titanium catalysed oxidation of aryl sulphide* ***108***

One drawback of this procedure is the competing formation of sulphone **111** as a by-product, which was shown to be present from the beginning of the reaction. It was discovered that there were two distinct asymmetric processes operating, one involving oxidation of the sulphide to the sulphoxide, and the other involving kinetic resolution *via* oxidation of the sulphoxide to the sulphone. Serendipitously, both processes work in tandem, resulting in an increased ee. It was found that the (*S*)-enantiomer of the sulphoxide was formed preferentially (29% ee when almost no sulphone is present), whilst the oxidation of the (*R*)-sulphoxide was faster, resulting in the (*S*)-enantiomer being formed in a higher enantioselectivity. This was confirmed by the kinetic resolution of racemic methyl *para*-tolyl sulphoxide, which afforded the recovered (*S*)-sulphoxide in 33% ee at 50% conversion.

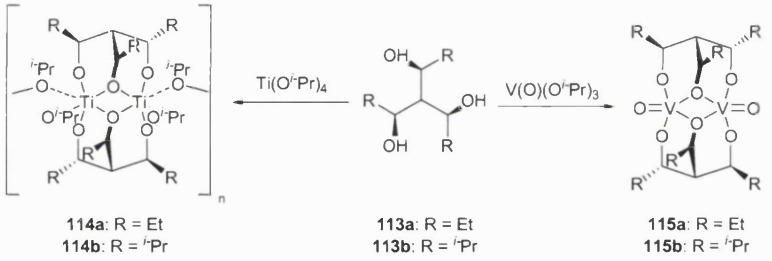
In 1999, it was reported that the enantioselectivities of sulphide oxidations were increased when a partially hydrolysed zirconium complex ($[[Zr_2(\mathbf{100b})_2(O^n\text{Bu})(OH)]\cdot nH_2O]_m$ (n = 3,4)) **112**, incorporating ligand **100b**, was used in place of the titanium complex.[84] These reactions required 2% catalyst loading and resulted in (*R*)-sulphoxide products in good enantioselectivities with the opposite configuration to

phenyl benzyl sulphide under these conditions resulted in (*R*)-sulphoxide **110** in 79% ee and 95% conversion (Scheme 33).




**Scheme 33** *Zirconium catalysed oxidation of aryl sulphide* ***108***

In 1997 Knochel, Sundermeyer *et al.* reported the use of $C_3$-symmetric triols **113a** and **113b** as ligands for vanadium and titanium complexes (Scheme 34).[54] The crystal structure of vanadium complex **115a** is depicted in Figure 43, which illustrates that the complex is not $C_3$-symmetric. The catalytic activity of these complexes was tested for a series of asymmetric transformations: the addition of diethyl zinc and trimethylsilyl cyanide to benzaldehyde **116**, and the oxidations of geraniol and ethyl phenyl sulphide with *tert*-butyl hydroperoxide (THBP). The results of the screening of the titanium complexes **114a** and **114b** are depicted in Scheme 35.




**Scheme 34** *$C_3$-Symmetric triol* ***113a-b*** *and the resulting titanium and vanadium complexes*

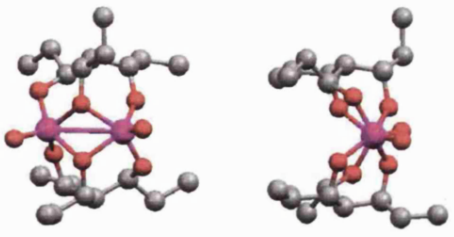
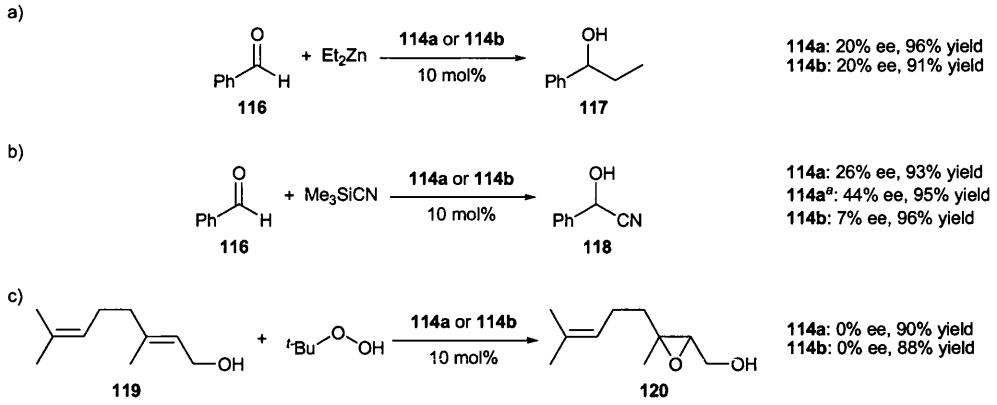


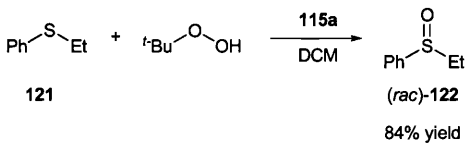
**Figure 43** *Two side views of the crystal structure of the vanadium complex* ***115a****, emphasising the non-$C_3$-symmetric character of the complex*




**Scheme 35** *Reactions catalysed by titanium complexes **114a** and **114b** ([a] 100 mol% catalyst)*

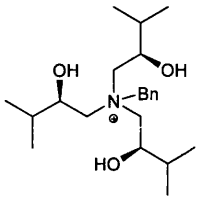
Both the titanium complexes **114a** and **114b** showed limited stereocontrol when screened in the addition reactions to benzaldehyde **116**, with both catalysts resulting in the addition alcohols **117** and **118** in poor enantioselectivities, but excellent yields (Scheme 35a, b). The oxidation of geraniol **119** with TBHP resulted in epoxide **120** in a good yield for both the catalysts (**114a**: 90%, **114b**: 88%), but no enantioselectivity was observed in either reaction (Scheme 35c). An oxidation of phenyl ethyl sulphide was also attempted, but neither complex showed any catalytic activity for this process.

The screening of vanadium complex **115a** (Figure 43) was then attempted, but no Lewis acid activity was observed in either of the addition reactions to benzaldehyde. However, when the reaction was screened in the TBHP oxidations, it was found to be an efficient catalyst. Geraniol was oxidised in the presence of 0.1 mol% of **115a** resulting in the racemic product in 96% yield, while the oxidation of phenyl ethyl sulphide was achieved in 4 hours, resulting in the product in 84% yield (Scheme 36). A range of other phenyl alkyl sulphides were successfully oxidised to afford racemic sulphoxides in good yields. Although, no chirality was induced in these transformations, it was found that when one equivalent of TBHP was used, only the sulphoxide (*rac*)-**122** was formed with no sulphone detected; but if 2.5 equivalents were used then complete conversion to the sulphone was observed.



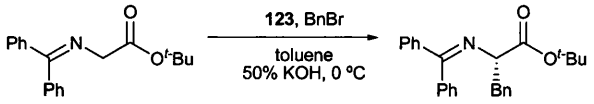

**Scheme 36** *Oxidation of phenyl ethyl sulphide **120** catalysed by vanadium complex **115a***

In 2003, Takabe *et al.* reported the use of amine based triol **123** as a chiral phase-transfer catalyst (Figure 44).[85] The application of this quaternary amine in the enantioselective alkylation of imine **38** with BnBr resulted in the alkylated product (*S*)-**124** in 58% ee and 55% yield (Scheme 37).




**123**

**Figure 44** *Quaternary amine based phase transfer catalyst (PTC)* ***123***




**38** (*S*)-**124**

58% ee
55% yield

**Scheme 37** *Enantioselective alkylation of imine* ***124*** *with BnBr using chiral PTC* ***123***

The hydrogen bonding in the transition state between a hydroxyl group of **123** and the nitrogen of the *E*-enolate of the imine is postulated to be responsible for the enantioselectivity of the reaction, forming a 9-membered transition state (Figure 45). Benzyl bromide therefore approaches from the less hindered *re*-face affording (*S*)-**124**.

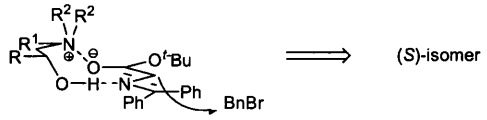
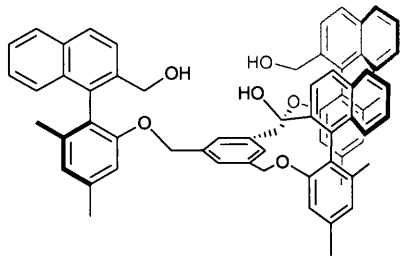


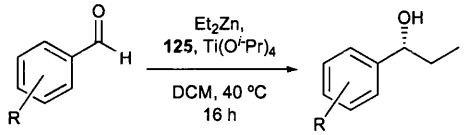

**Figure 45** *Proposed transition state*

$C_3$-Symmetric triol **125** containing three axially chiral biaryl units has been reported as an effective ligand in the titanium mediated enantioselective addition of diethyl zinc to aromatic aldehydes.[86] Treatment of aromatic aldehydes **126a-f** with three equivalents of diethyl zinc in the presence of 20 mol% of triol **125** and 1.4 equivalents of titanium tetra *iso*-propoxide, resulted in (*R*)-alcohols **127a-f** in excellent enantioselectivities and yields (Scheme 38, Table 22). It was found that the reaction only proceeded to a quantitative conversion when an excess of titanium tetra *iso*-propoxide was used; a stoichiometric amount resulted in only trace amounts of the product.



125

**Figure 46** *$C_3$-Symmetric triol* ***125***



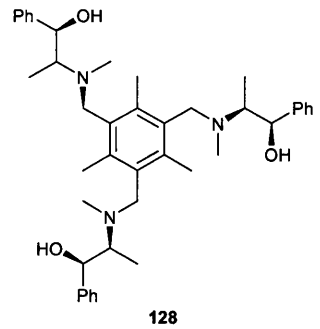

126 (*R*)-127a-f

**Scheme 38** *Titanium mediated addition of diethyl zinc to aromatic aldehydes* ***127a-f***

**Table 22**

| Alcohol | R | Yield /% | ee /% |
|---|---|---|---|
| **127a** | H | 93 | 90 |
| **127b** | 4-MeO | 97 | 96 |
| **127c** | 2-MeO | 81 | 96 |
| **127d** | 2-Cl | 91 | 94 |
| **127e** | 3,5-MeO | 94 | 96 |
| **127f** | 4-Me | 95 | 98 |

Armstrong *et al.* have also reported the use of a complex derived from triol **128** (Figure 47) and titanium *iso*-propoxide to catalyse the addition of diethyl zinc to benzaldehyde.[87] However, (*R*)-1-phenylpropan-1-ol **127a** was obtained in a poor 10% ee even when eleven equivalents of titanium *iso*-propoxide were used.

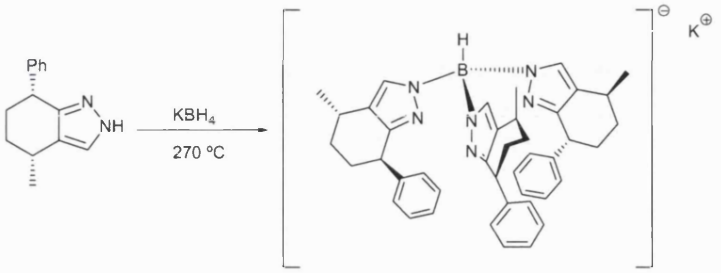


128

**Figure 47** *Triol* ***128***

### Nitrogen Tripodal Ligands

The elaboration of enantiomerically pure pyrazoles into enantiopure multidentate $C_1$, $C_2$ and $C_3$-symmetric tris-(pyroazolyl)hydroborate ligands was reported by Tolman *et al.*[88] Work was focussed on the formation of a multi-dentate ligand from *cis*-**129**, in which treatment with potassium borohydride at 270 °C resulted in the formation of the potassium borohydride salt of **130** (Scheme 39).




*cis*-**129** K(**130**)

**Scheme 39** *Formation of ligand K-(**130**) from cis-**129***

Analysis of both the $^{1}H$ and the $^{13}C$ NMR spectra revealed that there was only one pyrazole environment present implying that the molecule displays 3-fold symmetry. This was confirmed by the X-ray crystal structure of the Cu(I) complex **131** (Figure 48). This also revealed that the pyrazole groups all had *trans*-stereochemistry, indicating that epimerisation had occurred at the three activated benzylic positions of the chiral ligand. Pyrazole **130** was also converted into neutral tridentate phosphine oxides, but these exhibited much lower chiral induction.

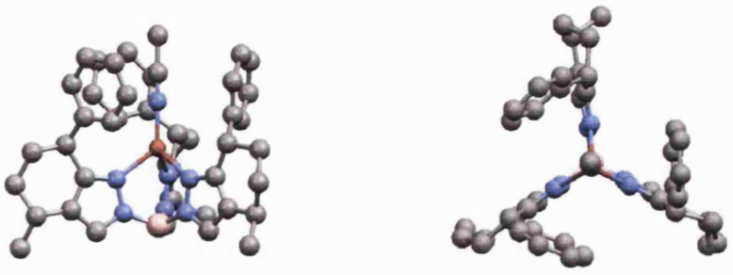
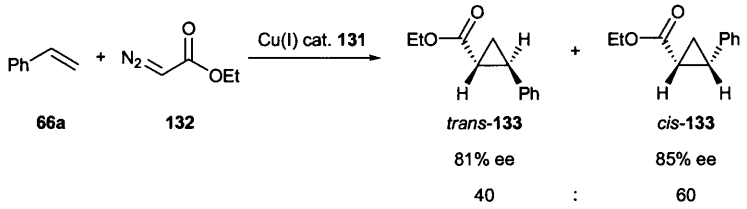


**Figure 48** *Side and top views of the X-ray crystal structure of (**130**)-Cu($CH_3CN$)·$CH_2Cl_2$ complex **131** (hydrogens and $CH_2Cl_2$ omitted for clarity)*

Copper complexes with this type of ligand were used to catalyse the cyclopropanation of styrene **66a** by ethyldiazoacetate **132**. It was found that complex **131** produced the best results, giving *trans*-(1*R*,2*R*) cyclopropane **133** in 81% ee and cyclopropane *cis*-(1*R*,2*S*)-**133** in 85% ee in a *trans*:*cis* ratio of 40:60 (Scheme 40).




**Scheme 40** *Copper catalysed cyclopropanation of styrene* ***66a*** *by ethyldiazoacetate* ***132***

This is the first example of a tris-(pyrazolyl)hydroborate system inducing high level of asymmetric induction in a catalytic reaction, although the enantioselectivities are still less than the highest reported for alternate $C_2$-symmetric bisoxazoline ligands (99% ee *trans*, 97% ee *cis*).[89]

The application of the dinuclear manganese complex of TP-TACN **134** (Figure 49) in the epoxidation of vinyl arenes, using $H_2O_2$ as an oxidant (Scheme 41), has been reported by Bolm *et al.*[90] Treatment of styrene **66a** in the presence of 2 mol% of complex **135** resulted in 28% conversion giving epoxide **136** with 24% ee after 2 hours. When the reaction time was extended to 4 hours the conversion increased (88%), but the enantioselectivity was reduced (15%).

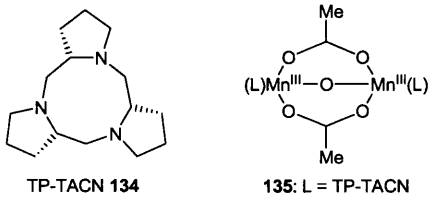
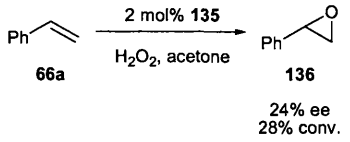
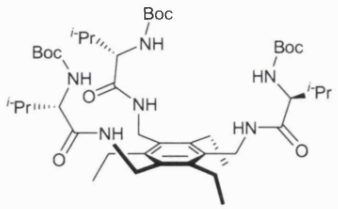



**Figure 49** *TP-TACN* ***134*** *and its dinuclear manganese complex* ***135***



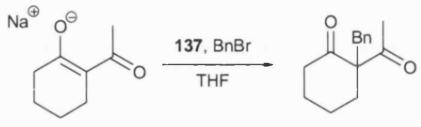

**Scheme 41** *Epoxidation of styrene 66a with (TP-TACN)Mn* ***135***

Postnikova *et al.* have reported the use of a chiral $C_3$-symmetric receptor **137** (Figure 50) for the enantioselective alkylation of the sodium enolates of cyclic β-diketones such as **138** with benzyl bromide.[91] For example, alkylated β-diketone **139** was obtained in 42% ee, the stereochemistry of which was not defined (Scheme 42).



137

**Figure 50** *$C_3$-Symmetric receptor **137***




138 139

42% ee
40% yield

**Scheme 42** *Enantioselective alkylation of the sodium enolates of cyclic β-diketone **138** catalysed by receptor **137***

Gade *et al.* reported the use of zirconium complexes **140a** and **140b** (Figure 51) as catalysts for the alkylation of aryl aldehydes and ketones (Scheme 43, Table 23).[70] It was found that the methylation of aryl ketones **141a-c** with complex (*S,S,S*)-**140a** proceeded with poor stereoselectivity (0-40% ee) (Table 23, entry 1-3), though the alcohol products from the methylation of aldehydes **141d-g** were obtained with better stereocontrol (68-80%) (Table 23, 4-7). When complex (*R,R,R*)-**140b** was used for the methylation of 2-naphthyl aldehyde **141g**, alcohol (*R*)-**142g** was obtained in a high 82% ee (Table 23, entry 8).

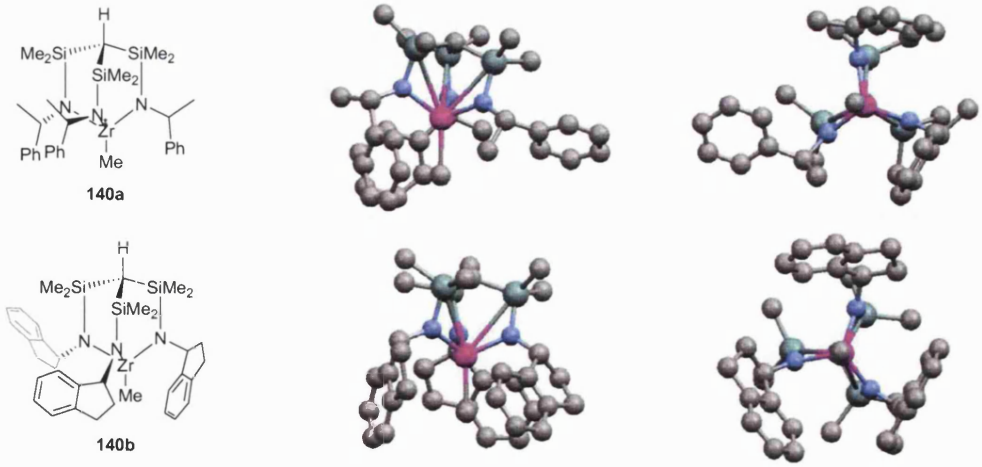
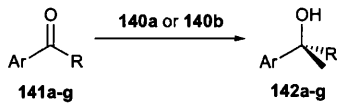



**Figure 51** *Complexes (S,S,S)-**140a** and (R,R,R)-**140b** and side and top views of their X-ray crystal structures (left and right respectively) (hydrogens omitted for clarity)*




141a-g 142a-g

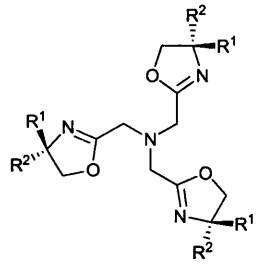
**Scheme 43** *Alkylation of aryl aldehydes* ***141a-g*** *catalysed by* ***140a*** *and* ***140b***

**Table 23**

| Entry | Alcohol | Ar | R | Catalyst | ee /% | Configuration |
|---|---|---|---|---|---|---|
| 1 | **142a** | Ph | PhCH=CH | **140a** | 0 | *S* |
| 2 | **142b** | Ph | $^{i}$Pr | **140a** | 12 | *S* |
| 3 | **142c** | Ph | Et | **140a** | 40 | *S* |
| 4 | **142d** | Ph | H | **140a** | 76 | *S* |
| 5 | **142e** | 4-F($C_6H_4$) | H | **140a** | 74 | *S* |
| 6 | **142f** | 4-Cl($C_6H_4$) | H | **140a** | 68 | *S* |
| 7 | **142g** | 2-naphthyl | H | **140a** | 80 | *S* |
| 8 | **142g** | 2-naphthyl | H | **140b** | 82 | *R* |

### Chiral Trisoxazolines as ligands for $C_3$-Symmetric complexes

In 1995 the use of amine based trisoxazolines **143a** and **143b** as ligands for the copper catalysed enantioselective allylic oxidation of cyclic alkenes, was described (Figure 52, Scheme 44, Table 24).[92]

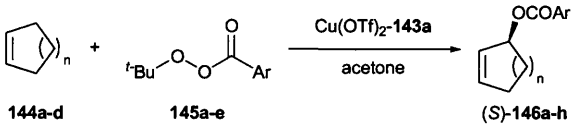



(*S*)-**143a**: $R^1$ = H, $R^2$ = Ph
(*R*)-**143a**: $R^1$ = Ph, $R^2$ = H
(*S*)-**143b**: $R^1$ = H, $R^2$ = $^{i}$Pr

**Figure 52** *Amine based tris(oxazolines)* ***143a*** *and* ***143b***

The copper(II) complex resulting from the treatment of amino-ligand (*S*)-**143a** with $Cu(OTf)_2$ was used to catalyse the oxidation of cyclopentene with *tert*-butyl perbenzoate affording the product, (*S*)-2-cyclopentenyl benzoate **144a** in 74% ee and 68% yield at room temperature (Table 24, entry 1). The enantioselectivity was increased to 88% when the temperature was lowered to -20 °C, though the yield was only 11% after 111 hours (Table 24, entry 3). The asymmetric induction arising from the use of the copper(II) complex of ligand (*S*)-**143b**, was inferior to that of $Cu(OTf)_2$·**143a**, affording allyl acetate (*S*)-**146a** in only 23% ee at room temperature.

The oxidation of other cyclic alkenes was also examined, resulting in the products in poor to good enantioselectivities (Table 24, Entries 4-8). In 1997, this study was further extended to determine the effect that the aryl substituent of the peroxyester oxidants had on the enantioselectivity of oxidation of cyclopentene using amino-catalyst (*R*)-**143a** (Table 24, Entries 9-14).[93] It was found that the introduction of *meta*- and *para*- substituents did not have much of an effect on the enantioselectivity, though the *para*-nitro group did have a dramatic detrimental effect on the reaction rate. The *ortho*-methoxy group resulted in (*S*)-**146a** in a slightly higher enantioselectivity (83%) (Table 24, entry 11), which increased when the reaction was performed at the lower temperature of -20 °C (91%) (Table 24, entry 13). The use of molecular sieves in the reaction was also found to improve the rate of the reaction, without a negative effect on the enantioselectivity.



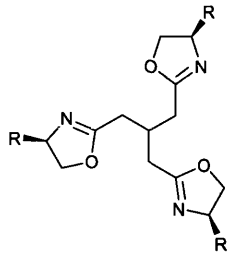

**Scheme 44** *Enantioselective allylic oxidation of **144a-d** catalysed by Cu(OTf)$_2$·**143a***

**Table 24**

| Entry | Product | n | Ar | T /°C | Time /h | Yield /% | ee /% |
|---|---|---|---|---|---|---|---|
| 1 | **146a** | 1 | Ph | rt | 40 | 68 | 74 |
| 2 | **146a** | 1 | Ph | 0 | 92 | 44 | 84 |
| 3 | **146a** | 1 | Ph | -20 | 111 | 11 | 88 |
| 4 | **146b** | 2 | Ph | rt | 48 | 11 | 56 |
| 5 | **146b** | 2 | Ph | 6 | 300 | 12 | 57 |
| 6 | **146b** | 2 | Ph | -20 | 670 | 10 | 69 |
| 7 | **146c** | 3 | Ph | rt | 90 | 34 | 14 |
| 8 | **146d** | 4 | Ph | rt | 90 | 18 | 54 |
| 9 | **146e** | 1 | 4-MeO($C_6H_4$) | rt | 17 | 55 | 68 |
| 10 | **146f** | 1 | 4-$NO_2$($C_6H_4$) | rt | 17 | - | - |
| 11 | **146g** | 1 | 2-MeO($C_6H_4$) | rt | 8 | 16 | 83 |
| 12 | **146g** | 1 | 2-MeO($C_6H_4$) | 0 | 27 | 22 | 87 |
| 13 | **146g** | 1 | 2-MeO($C_6H_4$) | -20 | 190 | 5 | 91 |
| 14 | **146h** | 1 | 3-MeO($C_6H_4$) | rt | 17 | 61 | 65 |

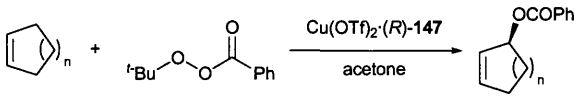
Three years later, Katsuki *et al.* reported the use of the carbon analogue (*R*)-**147** (Figure 53) as an efficient chiral auxiliary in the same allylic oxidations using *tert*-butyl perbenzoate as the oxidant, affording allylic acetate products with the opposite configuration, in higher enantioselectivity and shorter reaction times (Scheme 45, Table

25).[94] For example, the allylic oxidation of cyclopentene **144a** at room temperature resulted in (*R*)-benzoate **146a** in 80% ee and 71 % yield after 6 hours (Table 25, entry 1). The enantioselectivity was increased to 89% when the reaction was performed at -20 °C (Table 25, entry 3).




(*R*)-**147**: R = 4-MeOC$_6$H$_4$

**Figure 53** *Carbon based trisoxazoline ligand* ***147***




**144a-d** **145a** (*S*)-**146a-d**

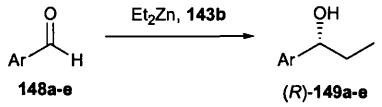
**Scheme 45** *Enantioselective allylic oxidation of* ***144a-d*** *catalysed by Cu(OTf)$_2$·(R)-****147***

**Table 25**

| Entry | Product | n | T /°C | Time /h | Yield /% | ee /% |
|---|---|---|---|---|---|---|
| 1 | **146a** | 1 | rt | 6 | 71 | 80 |
| 2 | **146a** | 1 | 0 | 48 | 73 | 85 |
| 3 | **146a** | 1 | -20 | 200 | 46 | 89 |
| 4 | **146b** | 2 | 0 | 48 | 80 | 82 |
| 5 | **146b** | 2 | -20 | 200 | 50 | 86 |
| 6 | **146c** | 3 | 0 | 48 | 64 | 88 |
| 7 | **146c** | 3 | -20 | 200 | 13 | 92 |
| 8 | **146d** | 4 | rt | 48 | 24 | 81 |
| 9 | **146d** | 4 | 0 | 200 | 25 | 85 |

Chan *et al.* reported the use of ligand **143b** (Figure 52) as the catalyst for the enantioselective addition of diethylzinc to aldehydes, to afford alcohol products with good enantioselectivity (72-90% ee) (Scheme 46, Table 26).[95] The best result was observed on treatment of 1-naphthylaldehyde **148c** with 20 mol% of **143b** and six equivalents of diethyl zinc which resulted in alcohol (*R*)-**149c** in 84% ee and 95% yield (Table 26, entry 5). It was found that reducing the number of equivalents of diethyl zinc, reduced the enantioselectivity and yield; using only two equivalents gave alcohol

(*R*)-**149a** in only 54% ee and 70% yield compared with 82% ee and 92% yield with six equivalents of diethyl zinc (Table 26, entries 1 and 2).



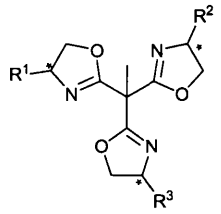

**Scheme 46** *Diethylzinc addition to aldehydes catalysed by* ***143b***

**Table 26**

| Entry | Product | Ar | Yield /% | ee /% |
|---|---|---|---|---|
| 1 | **149a** | Ph | 92 | 82 |
| 2 | **149a**[a] | Ph | 70 | 54 |
| 3 | **149b** | 2-MeO($C_6H_4$) | 95 | 72 |
| 4 | **149c** | 1-naphthyl | 95 | 84 |
| 5 | **149d** | 2-naphthyl | 90 | 78 |
| 6 | **149e** | 9-phenanthrene | 81 | 90 |

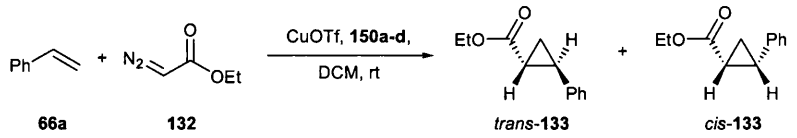
[a] 2 equivalents of $Et_2Zn$

In 2001, a modular approach to the synthesis of $C_1$ and $C_3$ chiral trisoxazoline based ligands **150a-d** and their application in the copper catalysed cyclopropanation of styrene was reported (Figure 54).[96] This approach allows the synthesis of trisoxazoline ligands with mixed substitution patterns. It was found that *pseudo*-$C_3$-symmetric ligand **150c** afforded the cyclopropanation products with the highest enantioselectivities (Table 27). For example, treatment of styrene **66a** with ethyl diazoacetate **132** in the presence of copper(I) triflate and ligand **150c** resulted in cyclopropyl products in a *trans*:*cis* ratio of 69:31, with the *trans*-cyclopropane product **133** in 86% ee, and *cis*-**133** in 81% ee (Table 27, entry 3).




(*S*)-**150a**: $R^1 = R^2 = R^3 = {}^i$Pr
(*S*)-**150b**: $R^1 = R^2 = {}^i$Pr, $R^3 = {}^t$Bu
(*S*)-**150c**: $R^1 = {}^i$Pr, $R^2 = R^3 = {}^t$Bu
(*S*)-**150d**: $R^1 = R^2 = R^3 = {}^t$Bu

**Figure 54** *Chiral trisoxazolines* ***150a-d***



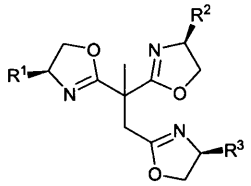

66a 132 *trans*-133 *cis*-133

**Scheme 47** *Copper catalysed cyclopropanation of styrene* ***66a*** *using oxazoline ligands* ***150a-d***

**Table 27**

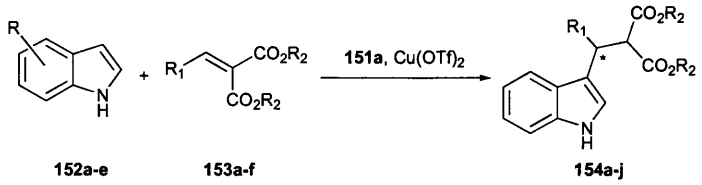
| Entry | Ligand | *cis* : *trans* | *trans*-134 ee /% | *cis*-134 ee /% |
|---|---|---|---|---|
| 1 | **150a** | 29 : 71 | 67 | 64 |
| 2 | **150b** | 29 : 71 | 78 | 72 |
| 3 | **150c** | 31 : 69 | 86 | 81 |
| 4 | **150d** | 31 : 69 | 70 | 68 |

More recently, the use of *pseudo-$C_3$*-symmetric chiral trisoxazolines **151d-f** (Figure 55) as ligands for the copper catalysed Friedel-Crafts alkylation of indoles with alkylidene malonates has been reported, resulting in both enantiomers of the alkylated indole products in high enantioselectivities (60-98%) (Scheme 48, Table 28).[97] The ligands were synthesised using a two-step procedure from trimethyl 1,2,2-propanetricarboxylate and the corresponding amino alcohol. $Cu(OTf)_2$ was used as the copper source as it gave enhanced enantioselectivity in more cases than $Cu(ClO_4)_2 \cdot 6H_2O$. Interestingly, the choice of solvent had a dramatic effect on the enantioselectivity of the reaction. It was found that alcohols accelerated the process, with bulkier alcohols providing better enantioselectivities; BuOH as a solvent resulted in (*S*)-**154a** in 98% ee and 99% yield at -25 °C (using ligand **151a**). Also the use of chlorinated solvents resulted in a reversal of the selectivity with 1,1,2,2-tetrachloroethane (TTCE) proving to be the best solvent for the synthesis of the (*R*)-enantiomer, giving (*R*)-indole **154a** in a 90% ee and 61% yield (Table 28, entry 1). Substituents on the indole ring were found to strongly influence the selectivity of the reaction, with 4- and 5-substituted indoles giving excellent enantioselectivities (Table 28, entries 1-3).



(*S*)-**151a**: $R^1 = R^2 = R^3 = {}^tBu$
(*S*)-**151b**: $R^1 = R^2 = {}^iPr$, $R^3 = {}^tBu$
(*S*)-**151c**: $R^1 = {}^iPr$, $R^2 = R^3 = {}^tBu$
(*S*)-**151d**: $R^1 = R^2 = R^3 = {}^iPr$
(*S*)-**151e**: $R^1 = R^2 = R^3 = {}^sBu$
(*R*)-**151f**: $R^1 = R^2 = R^3 = Ph$

**Figure 55** *Chiral trisoxazolines* ***151a-f***




**152a-e** **153a-f** **154a-j**

**Scheme 48** *Copper catalysed Friedel-Crafts alkylation of indoles* ***152a-e*** *with alkylidene malonates* ***153a-f*** *catalysed by pseudo-$C_3$-symmetric chiral trisoxazoline* ***151a***

**Table 28**

| Entry | Product | R | $R^1$ | $R^2$ | Condition A[a] | | Condition B[b] | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Yield /% | (*S*)-154 ee /% | Yield /% | (*R*)-154 ee /% |
| 1 | **154a** | 4-MeO | Ph | Et | 99 | 98 | 90 | 61 |
| 2 | **154b** | 5-MeO | Ph | Et | 79 | 94 | 67 | 60 |
| 3 | **154c** | 5-Me | Ph | Et | 89 | 95 | 75 | 73 |
| 4 | **154d** | 7-Me | Ph | Et | 82 | 89 | 90 | 56 |
| 5 | **154e** | H | Ph | Me | 99 | 94 | 86 | 80 |
| 6 | **154f** | H | Ph | Et | 99 | 91 | 83 | 65 |
| 7 | **154g** | H | Ph | $^iBu$ | 99 | 97 | 73 | 75 |
| 8 | **154h** | H | 2-Cl($C_6H_4$) | Et | 93 | 97 | 99 | 85 |
| 9 | **154i** | H | 3-$NO_2$($C_6H_4$) | Et | 99[c] | 83 | 99 | 89 |
| 10 | **154j** | H | 4-$NO_2$($C_6H_4$) | Et | 99[c] | 91 | 99 | 81 |

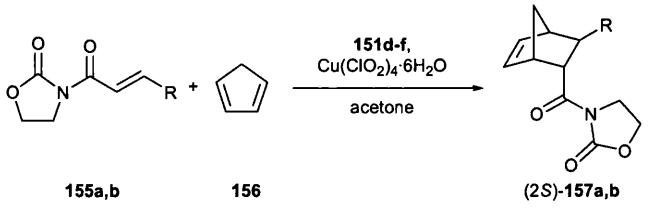
[a] Condition A: Reaction carried out in iso-butyl alcohol at -25 °C with air atmosphere; [b] Condition B: Reaction carried out in TTCE at 0 °C with $N_2$ atmosphere; [c] 0 °C.

A range of malonates were also screened in this process using ligand **151a** and $Cu(OTf)_2$ (Table 28, entries 5-10). It was found that the more bulky the ester group the higher the enantioselectivity, with *iso*-butyl esters providing the highest enantioselectivity and methyl ester giving the lowest. Other arylidene malonates were also tested and it was found that electron withdrawing substituents slowed the reaction rate in *iso*-butyl alcohol, whilst accelerating it in TTCE. When the strongly electron withdrawing nitro-group was used the reaction temperature, for the process carried out

in *iso*-butyl alcohol, needed to be increased from -25 °C to 0 °C in order for the reaction to proceed (Table 28, entry 9 and 10). It was noted that the *pseudo*-$C_3$-symmetric complexes that were formed in this process were not water sensitive and therefore the reactions could be performed under an air atmosphere.

In conclusion, this methodology affords a useful preparation of the alkylation adducts, which, using the principle stereodivergent catalysis, can be engineered to provide the (*R*)- or (*S*)- enantiomer, depending on the solvent used.

In the same year, Zhou *et al.* reported the use of the same family of ligands in copper catalysed Diels-Alder reactions.[98] It was found that in this case using $Cu(ClO_4)_2 \cdot 6H_2O$ as the copper source and acetone as the solvent resulted in the products with highest enantioselectivities (Scheme 49, Table 29). Ligands **151d-f** were screened in the Diels-Alder reaction between *N*-acryloyl-2-oxazolidinones **155a,b** and cyclopentadiene **156**. Ligand **151e** was found to promote the reaction most effectively, resulting in **157a** in a 75% ee and 99% yield with 93:7 *endo* selectivity at -20 °C (Table 29, entry 2). It was found that lowering the reaction temperature to -45 °C resulted in the (2*S*)-*endo*-product with a higher enantioselectivity (80% ee) and 99% yield (Table 29, entry 4). The reaction with **155b** was much slower, though it proceeded with high selectivity (81% ee) albeit with only 21% conversion after 48 hours (Table 29, entry 5). Increasing the temperature to 0 °C allowed 100% conversion, but the enantioselectivity dropped to 74% (Table 29, entry 6). Interestingly, ligand **150f** resulted in the product with the opposite enantiomer, although this was not elaborated further in the report (Table 29, entry 3).



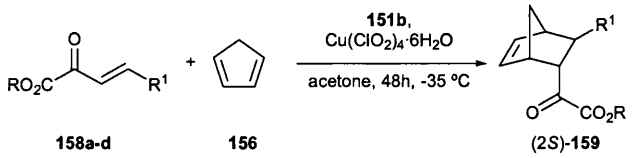

**Scheme 49** *Cu-catalysed Diels-Alder reactions between N-acryloyl-2-oxazolidinones **155a,b** and cyclopentadiene **156***

**Table 29**

| Entry | Product | R | Ligand | T /°C | Time /h | Yield /% | *exo* : *endo* | ee /% |
|---|---|---|---|---|---|---|---|---|
| 1 | **157a** | H | **150d** | -20 | 3 | 99 | 8 : 92 | 67 |
| 2 | **157a** | H | **150e** | -20 | 3 | 99 | 7 : 93 | 75 |
| 3 | **157a** | H | **150f** | -20 | 3 | 99 | 12 : 88 | 41[a] |
| 4 | **157a** | H | **150e** | -45 | 6 | 99 | 4 : 96 | 80 |
| 5 | **157b** | Me | **150e** | -20 | 48 | 21 | 10 : 90 | 81 |
| 6 | **157b** | Me | **150e** | 0 | 48 | 99 | 19 : 81 | 74 |

[a] Opposite enantiomer

The Diels-Alder reactions between keto-esters **158a-d** and cyclopentadiene **156** were also attempted. These proceeded with good enantioselectivities (up to 71% ee) and good yields (47-82%) (Scheme 50, Table 30). For example, the reaction of keto-ester **158a** resulted in bicyclic **159a** in 71% ee, 94% de and 64% yield (Table 30, entry 1). The substituted aryl ketone **158d** could not be resolved into its diastereomers and enantiomers, and therefore the enantioselectivity could not be determined.




158a-d 156 (2*S*)-159

**Scheme 50** *Cu-catalysed Diels-Alder reaction between keto-esters **158a-d** and cyclopentadiene **156***

**Table 30**

| Product | R | $R^1$ | Yield /% | *exo* : *endo* | ee /% |
|---|---|---|---|---|---|
| **159a** | Me | Ph | 64 | 3 : 97 | 71 |
| **159b** | Et | Ph | 82 | 3 : 97 | 64 |
| **159c** | Bn | Ph | 47 | 3 : 97 | 62 |
| **159d** | Me | 4-Br($C_6H_4$) | 56 | - | - |

The transition state was proposed to proceed *via* a distorted octahedral geometry around a copper complex, that would result in the *si* face of the acryloyl-2-oxazolidinone being blocked by the *iso*-butyl group of the ligand, resulting in attack from the *re* face to afford the (*S*)-enantiomer (Figure 56). A model to explain the stereochemistry of the products from reaction of cyclopentadiene with keto-esters was not proposed.

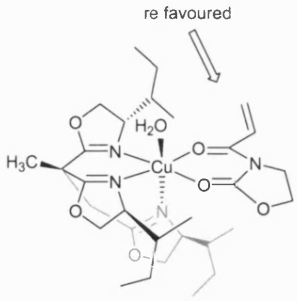
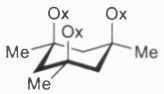
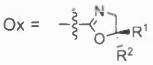



**Figure 56** *Distorted octahedral transition state*

In 2000, Bolm *et al.* reported the synthesis and application of trisoxazolines **160a-d** for both the diethyl zinc addition to benzaldehyde, and the allylic oxidation of cyclopentene (Figure 57).[99]

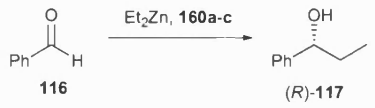



Ox = 

**160a**:$R^1$ = Me, $R^2$ = H
**160b**: $R^1$ = $^i$Pr, $R^2$ = H
**160c**: $R^1$ = $^t$Bu, $R^2$ = H
**160d**: $R^1$ = H, $R^2$ = Ph

**Figure 57** *Trisoxazolidine ligands **160a-d***

The use of trisoxazolines **160a-c** for the diethyl zinc addition to benzaldehyde **116** resulted in (*R*)-alcohol **117** with moderate enantioselectivities (33-43% ee) (Scheme 46, Table 31). Interestingly, trisoxazolines **160a** and **160b** resulted in predominantly (*R*)-1-phenyl propanol **117** (Table 31, entries 1 and 2), whilst **160c** yielded the (*S*)-enantiomer (Table 31, entry 3), with no explanation offered for this change in selectivity.

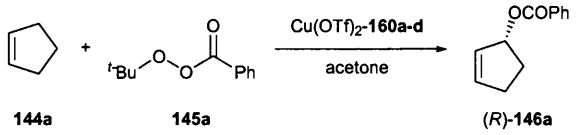



**Scheme 51** *Diethylzinc addition to aldehydes catalysed by **160a-c***

**Table 31**

| Entry | Ligand | Yield /% | ee /% | Configuration |
|---|---|---|---|---|
| 1 | **160a** | 75 | 36 | *R* |
| 2 | **160b** | 46 | 43 | *R* |
| 3 | **160c** | 75 | 33 | *S* |

The reaction conditions for the allylic oxidation of cyclopentene were optimised with the copper(II) complex of trisoxazoline **160a** (Scheme 44, Table 32). As with the amine based tris(oxazolines) system it was found that the addition of molecular sieves increased the reaction time, whilst the enantioselectivity was slightly enhanced at lower temperatures (-20 °C), resulting in (*S*)-2-cyclopentenyl benzoate **146a** in 48% ee and 31% yield after 92 hours (Table 32, entry 1). At 4 °C the reaction proceeded with a yield of 94%, but the enantioselectivity remained low at 45% (Table 32, entry 2). The other ligands were also applied using these conditions, with the (*R*)-alcohol being obtained in poor to moderate enantioselectivity (3-49%) in each case (Table 32, entries 3-6).

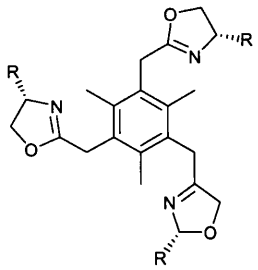



**Scheme 52** *Enantioselective allylic oxidation of cyclopentene catalysed by Cu(OTf)$_2$·**160a-d***

**Table 32**

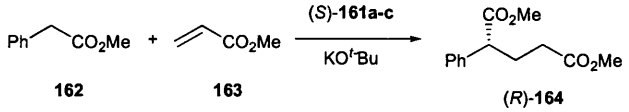
| Entry | Ligand | T /°C | Time /h | Yield /% | ee /% | Configuration |
|---|---|---|---|---|---|---|
| 1 | **160a** | -20 | 92 | 31 | 48 | *S* |
| 2 | **160a** | 4 | 40 | 94 | 45 | *S* |
| 3 | **160b** | -20 | 92 | 29 | 49 | *R* |
| 4 | **160c** | -20 | 252 | 17 | 43 | *R* |
| 5 | **160c** | 4 | 40 | 51 | 31 | *R* |
| 6 | **160d** | -20 | 92 | 12 | 3 | *R* |

In 2001, S-G. Kim *et al.* reported the use of aryl based $C_3$-symmetric chiral tris(oxazoline) derivatives (*S*)-**161a-c** (Figure 58) as ligands for the enantioselective conjugate addition between methyl phenylacetate **162** and methyl acrylate **163** (Scheme 53, Table 33).[100] Treatment of ester **162** with potassium *tert*-butoxide followed by ligands **161a-c** and then methyl acrylate resulted in the Michael addition product (*R*)-**164** in moderate to good ee. The best result was obtained with ligand **161a** with the diester (*R*)-**164** being obtained in 82% ee and 83% yield (Table 33, entry 1), which is comparable to the best results obtained for this transformation thus far.[101] Interestingly, the reaction did not proceed when sodium *tert*-butoxide was used in the place of potassium *tert*-butoxide, indicating that the reaction is likely to be catalysed by a tripodal potassium complex of ligand **161**.



(*S*)-**161a**: R = $^{i}$Pr
(*S*)-**161b**: R = $^{t}$Bu
(*S*)-**161c**: R = Ph

**Figure 58** *Benzene based $C_3$-symmetric chiral trisoxazoline derivatives (S)-**161a-c***



**162** **163** (*R*)-**164**

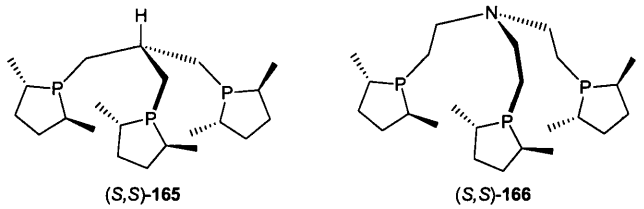
**Scheme 53** *Enantioselective Michael addition catalysed by ligand (S)-**161a-c** and KO$^{t}$Bu*

**Table 33**

| Ligand | Time /h | ee /% | Yield /% |
|---|---|---|---|
| **161a** | 8 | 82 | 83 |
| **161b** | 3 | 41 | 85 |
| **161c** | 3 | 56 | 80 |

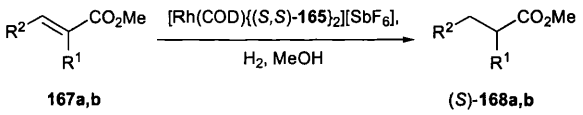
### Phosphorus Containing Ligands and Catalysts

In 1991, Burk *et al.* reported the development of chiral $C_3$-symmetric phosphine ligands **165** and **166** and the application of their rhodium complexes to the asymmetric hydrogenation of alkenes (Scheme 54, Table 34).[102] When screened for the hydrogenation of methyl acetamidocinnamate **167a**, (*S,S*)-**165** resulted in (*S*)-ester **168a** in 89% ee despite requiring quite a high reaction temperature (50 °C) (Table 34, entry 1), while (*S,S*)-**166** did not exhibit any catalytic activity. Increasing the temperature to 65 °C, in order to attempt to shorten the reaction time, resulted in the product **168a** in only 40% ee (Table 34, entry 2). The hydrogenation of dimethyl itaconate was also performed, resulting in (*S*)-ester **168b** in 94% ee (Table 34, entry 3).



(*S,S*)-**165** (*S,S*)-**166**

**Figure 59** *$C_3$-Symmetric phosphine ligands (S,S)-**165** and (S,S)-**166***



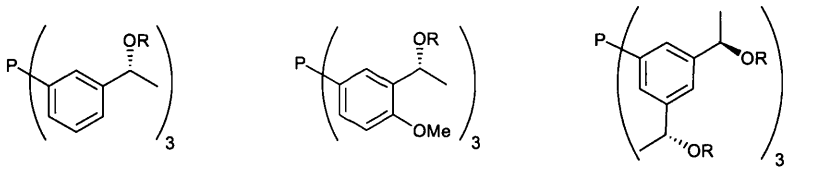

167a,b (S)-168a,b

**Scheme 54** *Asymmetric hydrogenation catalysed by a rhodium (S,S)-**165** complex*

**Table 34**

| Entry | Product | $R^1$ | $R^2$ | Time /h | T /°C | ee /% |
|---|---|---|---|---|---|---|
| 1 | **168a** | NHCOMe | Ph | 72 | 50 | 89 |
| 2 | **168a** | NHCOMe | Ph | 48 | 65 | 40 |
| 3 | **168b** | $CH_2CO_2Me$ | H | 20 | 50 | 94 |

In 2001, Burgess *et al.* reported the further development of a novel class of mono-dentate tri-arylphosphine $C_3$-symmetric ligands **169a-c**, **170a-c** and **171a-c** to test the efficacy of propeller-shaped $C_3$-symmetric ligands, that were first described in 1998 (Figure 60).[103] The ligands were screened in four palladium catalysed allylation reactions depicted in Scheme 55a-d, and the best results for each class of ligand are reported for each transformation. It was found that ligands **169-171** gave the highest enantioselectivities for cyclic structures (up to 82%), which compare favourably with previously reported results. However, the reaction using 1,3-diphenylpropenyl acetate resulted in substitution product in relatively poor selectivity (up to 32%) compared with several previously reported systems that afforded enantioselectivities of >99%.[104]



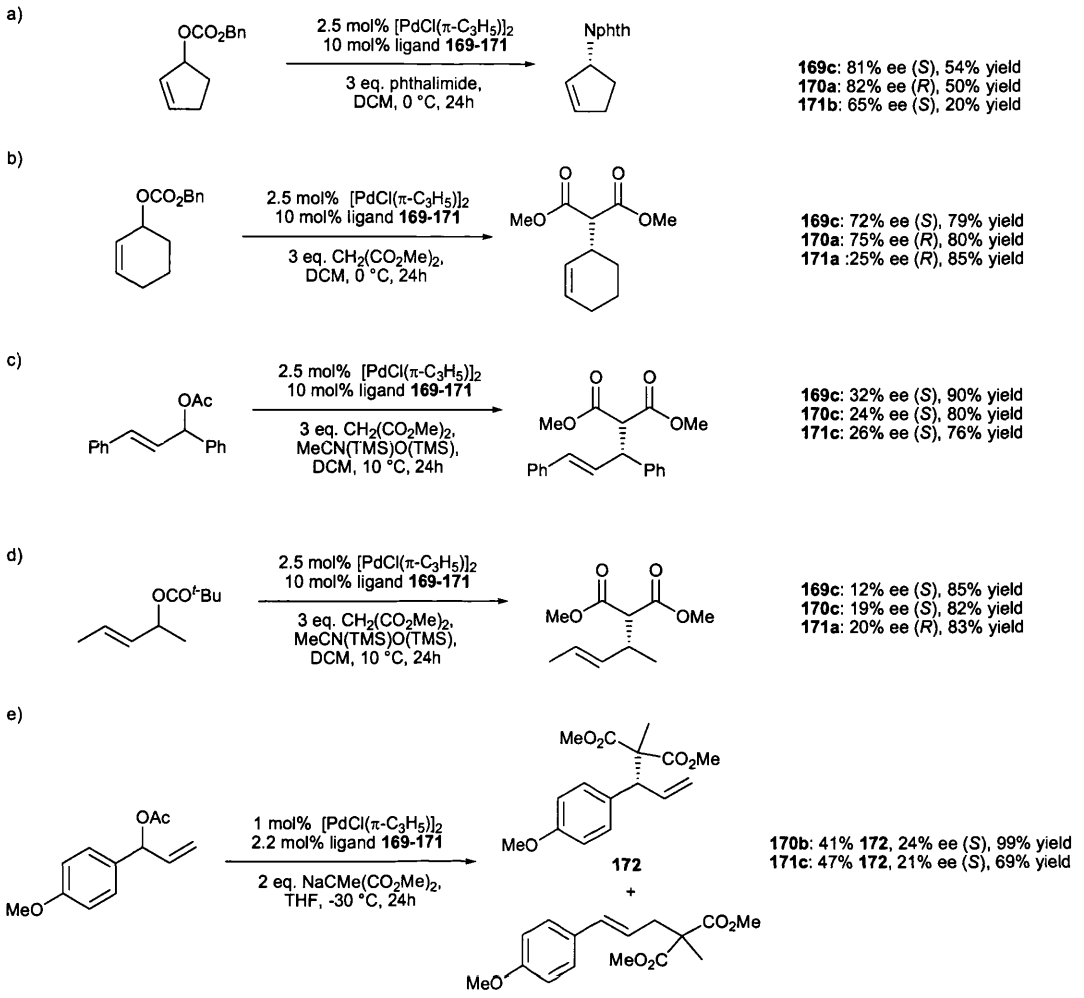

(*R*)-**169a**: R = Me
(*S*)-**169b**: R = Ph
(*S*)-**169c**: R = 2,6-$Me_2(C_6H_3)$

(*R*)-**170a**: R = Me
(*S*)-**170b**: R = Ph
(*S*)-**170c**: R = 2,6-$Me_2(C_6H_3)$

(*R,R*)-**171a**: R = Me
(*S,S*)-**171b**: R = Ph
(*S,S*)-**171c**: R = 2,6-$Me_2(C_6H_3)$

**Figure 60** *Phosphine Ligands **169-171a-c***

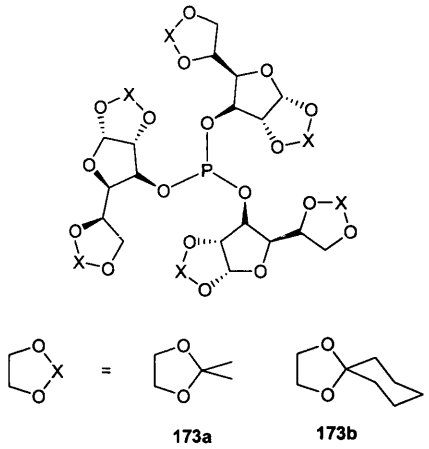
The more sterically demanding ligands (**170** and **171**) were also screened using transformation (e) (Scheme 55). The regioselectivity of the allylation is controlled by the *trans*-directing effect of the phosphine, which can lead to high regioselectivity for the internal allylation product. The best regioselectivity for the internal isomer resulted from the use of **171c**, giving an internal:terminal ratio of 47:53. However, the ee of the internal isomer **172** was only 24% using ligand **171a** under these conditions, compared with a previously reported enantiomeric excess of >90%.




**Scheme 55** *Range of transformations catalysed by ligands* ***169-171a-c***

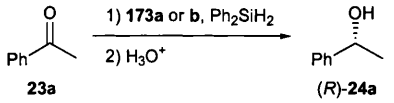
In 2001, Pizzano *et al.* reported the use of a previously reported[105] $C_3$-symmetric phosphite (Figure 61) as a ligand in the rhodium catalysed enantioselective hydrosilylation of acetophenone **23a** (Scheme 56, Table 35).[106] The optimal rhodium source was found to be the ethylene dimer $[Rh(\mu\text{-}Cl)(C_2H_4)_2]_2$. When the reaction was performed with a Rh:P-ligand ratio of 1:1, (*R*)-alcohol **24a** was obtained in a poor ee of only 7% using ligand **173a** (Table 35, entry 1); however, when the ratio was increased to 1:2 the enantioselectivity was substantially increased to 41% (Table 35, entry 2). The addition of a third equivalent lead to a further increase in enantioselectivity to 51%, but increasing the ratio to 1:4 and 1:5 had a detrimental effect on both the conversion and the enantioselectivity (Table 35, entries 3 and 4). These results imply that the catalytically active species in these reactions has three phosphite ligands per rhodium centre. The reactivity of ligand **173b** was also examined and it was found that this

ligand with bulkier cyclohexylidene substituents afforded the alcohol in an enhanced enantioselectivity of 58% ee (Table 35, entry 5).



173a 173b

**Figure 61** *$C_3$-Symmetric phosphite ligands ($P(DAG)_3$)* ***173a*** *and* ***173b***



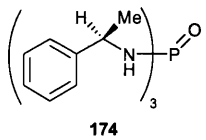
23a (*R*)-24a

**Scheme 56** *Enantioselective rhodium catalysed hydrosilylation of acetophenone* ***23a***

**Table 35**

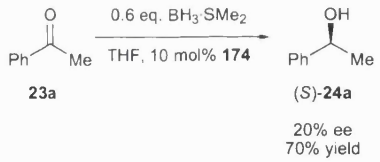
| Entry | Catalyst precursor | Ligand | Conversion /% | (*R*)-24a ee /% |
|---|---|---|---|---|
| 1 | ½[RhCl(C2H4)2]2 + P(DAG)3 | **173a** | 92 | 7 |
| 2 | ½[RhCl(C2H4)2]2 + 2 P(DAG)3 | **173a** | 96 | 41 |
| 3 | | **173b** | 92 | 52 |
| 4 | ½[RhCl(C2H4)2]2 + 3 P(DAG)3 | **173a** | 89 | 51 |
| 5 | | **173b** | 94 | 58 |

A novel class of catalyst containing the N-P=O unit was reported for the asymmetric reduction of ketones using borane as the reductant.[107] The $C_3$-symmetric catalyst **174** (Figure 62) was used in the borane reduction of acetophenone resulting in (*S*)-1-phenylethanol **24a** in 20% ee and 70% yield in only one hour (Scheme 57).



174

**Figure 62** *$C_3$-symmetric catalyst* ***174***




**Scheme 57** *Asymmetric reduction of acetophenone* ***23a*** *catalysed by (S)-****24a***

In 2004, Leung *et al.* reported the synthesis of a chiral $C_3$-symmetric phosphine oxide tripodal cobalt complex **175** derived from enantiomerically pure 1,1'-bi-2-naphthol (Figure 63), which was recrystallised from acetone/THF to afford the bis(diacetone alcohol) adduct Na((S)-**175**)$(C_6H_{12}O_2)_2$ (where $C_6H_{12}O_2$ = $MeCOCH_2CMe_2OH$).[108] Analysis of the X-ray crystal structure of this complex revealed the ligand's $C_3$-symmetric nature (Figure 64).

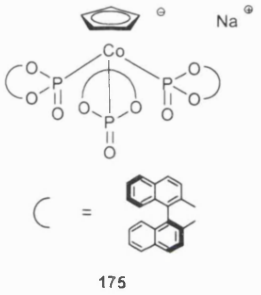



**Figure 63** *$C_3$-Symmetric tripodal ligand Na((S)-****175****)*

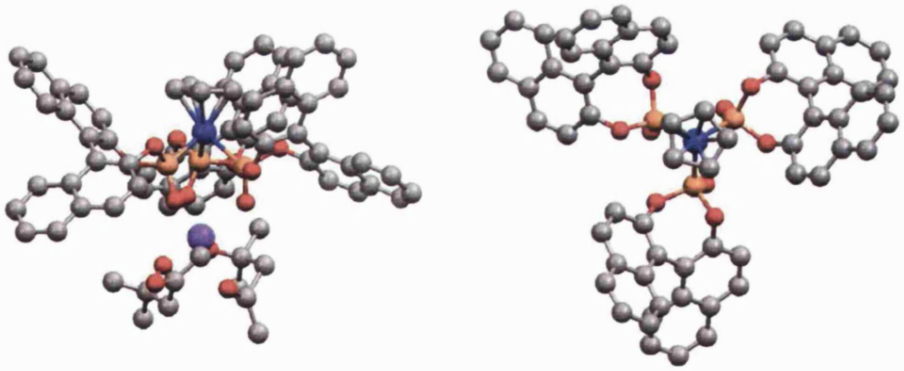
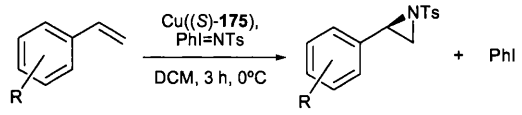


**Figure 64** *Top and side views of the Na((S)-****175****)$(C_6H_{12}O_2)_2$ complex (left and right respectively). Hydrogens omitted for clarity and Na$(C_6H_{12}O_2)_2$ also omitted from the top view to emphasise the $C_3$-symmetric nature of the ligand.*

The catalytic activity of Na((*S*)-**175**) was investigated for the copper catalysed aziridination of alkenes with PhI=NTs (Scheme 58, Table 36) *via* treatment of styrene **176a** with PhI=NTs in the presence of 5 mol% of a Cu catalyst prepared *in situ* from mixing $[Cu(MeCN)_4][BF_4]$ and Na((*S*)-**175**), resulting in aziridine **177** in 41% ee and

85% yield (Table 36, entry 1). It was found that the enantioselectivity increased when electron-withdrawing substituents were present on the styrene, for example aziridination of 4-chlorostyrene **176d** proceeded with 67% ee (Table 36, entry 4), whilst the product of 4-methylstyrene **176f** was afforded in only 34% ee (Table 36, entry 6).




176a-f 177a-f

**Scheme 58** *Cu-catalysed asymmetric aziridation of substituted styrenes **176a-f***

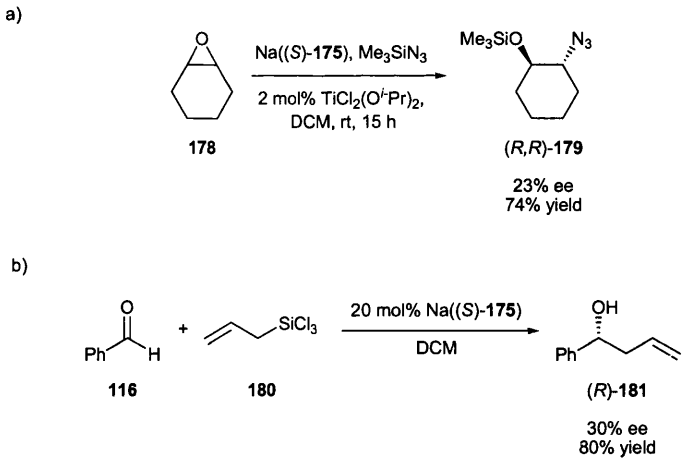
**Table 36**

| Product | R | Yield /% | ee /% |
|---|---|---|---|
| **177a** | H | 85 | 41 |
| **177b** | H | 88 | 43[a] |
| **177c** | 4-F | 82 | 32 |
| **177d** | 4-Cl | 82 | 61 |
| **177e** | 4-Br | 67 | 41 |
| **177f** | 4-Me | 77 | 34 |

[a]Na((*R*)-**175**) was used as the ligand to yield the opposite enantiomer.

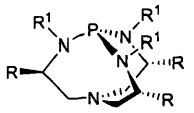
Ligand Na(*S*)-**175** has also been applied to the enantioselective ring opening of *meso*-epoxides. For example, treatment of Na((*S*)-**175**) with $Ti(O^{i}Pr)_2Cl_2$ resulted in an active catalyst which catalysed the ring opening of cyclohexene oxide **178** with $Me_3SiN_3$ to produce ((1*R*,2*R*)-2-azidocyclohexyloxy)trimethylsilane, (*R*,*R*)-**179**, in 23% ee and 74% yield (Scheme 59a).

The activity of Na(*S*)-**175** as a chiral Lewis base was also investigated for the allylation of benzaldehyde **116** with allyltrichlorosilane **180** in the presence of 20 mol% of Na((*S*)-**175**), affording (*R*)-1-phenylbut-3-en-1-ol (*R*)-**181** in a modest 30% ee and in 80% yield (Scheme 59b).




**Scheme 59** *Applications of Na((S)-**175**) in asymmetric catalysis: a) the asymmetric ring opening of epoxide **178** with $Me_3SiN_3$, b) the allylation of benzaldehyde **116***

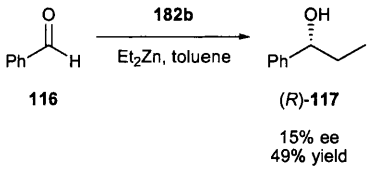
Proazaphosphatranes of the type **182a** (R = H, $R^1$ = alkyl, Bn, TMS) (Figure 65) are very strong non-ionic bases and catalysts that have been applied to several achiral base-catalysed transformations,[109] such as the Henry reaction,[110] acylation of alcohols,[111] *oxa*-Michael additions,[112] Wittig reactions,[113] and Suzuki cross-coupling reactions.[114] Their versatility and efficacy for a wide range of reactions has resulted in a lot of interest in the screening of their asymmetric analogues.



**182a**: R = H, $R^1$ = alkyl, Bn, TMS
**182b**: R = $R^1$ = $-(CH_2)_3-$
**182c**: R = Bn, $R^1$ = Me

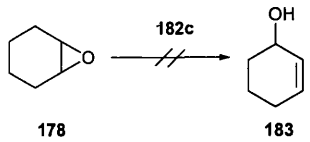
**Figure 65** *Proazaphosphantranes **182a-c***

In 1998, Yamamoto *et al.* reported the synthesis of the first asymmetric proazaphosphatrane **182b** based on (*S*)-proline (Figure 65).[115] The application of **182b** to the addition of diethyl zinc to benzaldehyde **116** resulted in (*R*)-**117** in a disappointing 15% ee and 49% yield (Scheme 60).




**Scheme 60** *Addition of diethyl zinc to benzaldehyde **116** catalysed by proazaphosphatrane **182b***

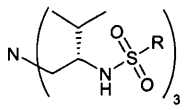
More recently, Verkade *et al.* have reported the synthesis of chiral proazaphosphatrane **182c** (Figure 65).[116] This was applied to the enantioselective deprotonation of cyclohexene oxide **178**; however, treatment with 0.2 equivalents of **182c** at room temperature for 27 hours, resulted in a negligible amount of 2-cyclohexenol **183** (Scheme 61); indicating that the proazaphosphatrane **182c** was not sufficiently basic to catalyse this reaction.




**Scheme 61** *Attempted enantioselective deprotonation of cyclohexene oxide with* ***182c***

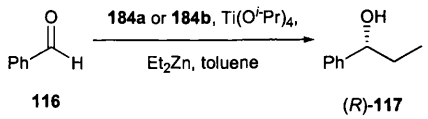
### Sulphonamide Ligands

Moberg *et al.* have reported the use of $C_3$-symmetric sulphonamides **184a** and **184b** as ligands for the titanium catalysed addition of diethyl zinc to benzaldehyde **116** (Figure 66, Scheme 62, Table 37).[117] Unfortunately, the alcohol was obtained in low selectivity with both ligands: ligand **184a** resulted in (*R*)-1-phenylethanol **117** in 31% ee at 96% conversion (Table 37, entry 2), whilst ligand **184b** gave the (*S*)-enantiomer in 11% ee at high conversion (97%) (Table 37, entry 4), but interestingly the (*R*)-enantiomer was formed in 17% ee at low conversions (29%) (Table 37, entry 3).




**184a**: R = 4-Me$C_6H_4$
**184b**: R = $CF_3$

**Figure 66** *Sulphonamide ligands* ***184a,b***




**116** **(*R*)-117**

**Scheme 62** *Titanium catalysed addition of diethyl zinc to benzaldehyde* ***116***

**Table 37**

| Entry | Ligand | Yield /% | ee of 117 /% | Conversion /% |
|---|---|---|---|---|
| 1 | **184a** | - | 25 (*R*) | 20 |
| 2 | **184a** | 91 | 31 (*R*) | 96 |
| 3 | **184b** | - | 17 (*R*) | 29 |
| 4 | **184b** | 89 | 11 (*S*) | 97 |

## 1.5 Conclusion

The potential of $C_3$-symmetric ligands to induce higher levels of stereocontrol in complexes than traditional $C_2$-symmetric ligands, has led to a flurry of publications in recent years. Unfortunately, as reported in this chapter, it has been found that many of the $C_3$-symmetric complexes that have been reported so far induce limited selectivity into organic asymmetric transformations. Therefore the aim of this project was to design and synthesise a $C_3$-symmetric ligand and its complex to be screened in a range of organic transformations in the hope that a high level of selectivity could be induced.

# CHAPTER 2:
# *Ligand Design*

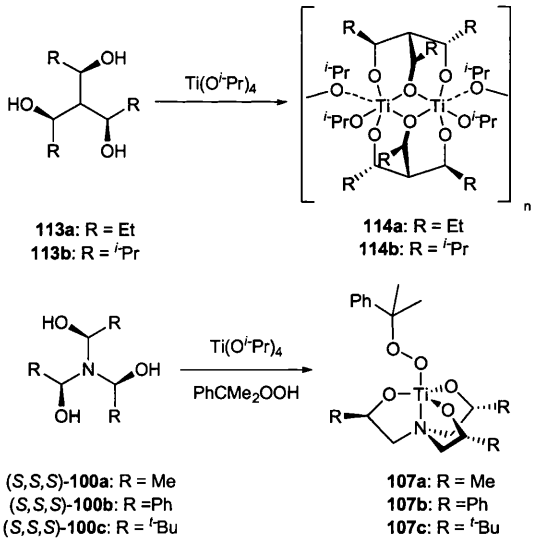
# 2 LIGAND DESIGN

## 2.1 Aims and Objectives

The aim of this work was to design and synthesise chiral monomeric $C_3$-symmetric complexes which could be used to catalyse a range of asymmetric transformations. It was hoped that the $C_3$-symmetric nature of these complexes would induce a high degree of chirality in a range of reactions; thus, making the complex competitive with known systems. Preliminary studies centred on the synthesis and screening of an achiral analogue, which was screened in a series of organic transformations to ensure that this family of complexes would prove effective as Lewis acid catalysts.

## 2.2 Advantages of Monomeric $C_3$-Symmetric Complexes

Complexes containing $C_3$-symmetric ligands have proved their potential as asymmetric catalysts (Chapter 1). However, as described, a potential problem that arises is the fact that the $C_3$-symmetry of the catalytically active complex formed from these types of ligands maybe lost, thus reducing the chiral relay potential of the ligand for asymmetric induction. A solution to this is to ensure that the complex forms a monomeric species, hence preserving the $C_3$-symmetric nature of the ligand, which consequently should induce higher levels of enantioselectivity. An example which highlights the potential reactivity differences between monomeric and oligomeric species is the difference in catalytic activity observed between the oligomeric titanium complex of triol **113**,[54] and the monomeric titanium complex of its amino analogue **100** (Scheme 63).[83]




**113a**: R = Et
**113b**: R = $^i$Pr

**114a**: R = Et
**114b**: R = $^i$Pr

(*S,S,S*)-**100a**: R = Me
(*S,S,S*)-**100b**: R =Ph
(*S,S,S*)-**100c**: R = $^t$Bu

**107a**: R = Me
**107b**: R =Ph
**107c**: R = $^t$Bu

**Scheme 63** *Complexes of triol **113** and amino triol **100***

Complexes **114a** and **114b** were shown to be fluxional on the NMR time scale indicating that even at low temperatures there is a mixture of species that are inter-converting *via* bridging alkoxide intermediates. Application of titanium complex **114a** in the oxidation of ethyl phenyl sulphide with *tert*-butyl hydroperoxide was unsuccessful, with no product being detected. A vanadium complex of ligand **113a**, which was proven to be an unsymmetrical binuclear species (Figure 67), catalysed the reaction, but no enantioselectivity was observed (Scheme 64 and *vide supra* 1.4.3).

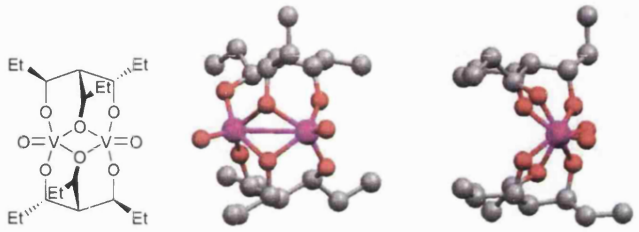
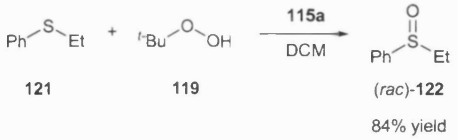
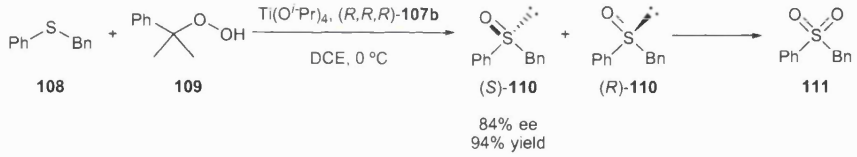


**Figure 67** *Vanadium complex **115a** and its X-ray crystal structure*




**Scheme 64** *Oxidation of ethyl phenyl sulphide catalysed by vanadium complex **115a***

Monomeric titanium complex (*R,R,R*)-**107b** was found to catalyse the oxidation of alkyl phenyl sulphides. The best results were observed using cumyl hydroperoxide as the oxidant, affording (*S*)-phenyl benzyl sulphoxide **110** in 84% ee and 94% yield (Scheme 65).




**Scheme 65** *Titanium catalysed oxidation of aryl sulphide **108***

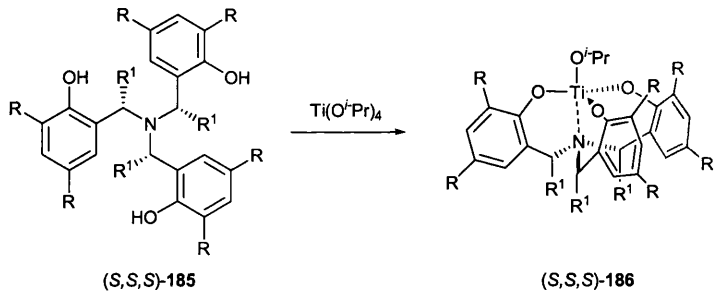
Sulphone **111** was found to be a side product in this reaction and its formation was proven to proceed *via* a kinetic resolution in which the (*R*)-enantiomer of the sulphoxide was preferentially oxidised to the sulphone, which can clearly improve the enantioselectivity of the recovered sulphoxide (*S*)-**110** as the reaction proceeds. Further studies revealed that the (*S*)-sulphoxide was formed in preference to the (*R*)-enantiomer (29% ee when almost no sulphone present), whilst the kinetic resolution of racemic

methyl *para*-tolyl sulphoxide resulted in recovered (*S*)-sulphoxide in 33% ee at 50% conversion.

Although the enantioselectivity observed in the reactions catalysed by the monomeric titanium species ranges from poor to acceptable, it is clear that the monomeric titanium complex **107a** is more active than the oligomeric titanium complex **114a**, which did not catalyse this transformation. In the case of the vanadium complex **115a**, its use resulted in racemic products. In fact, the levels of stereo-control in these sulphoxidation reactions are surprisingly high, given that the large stereo-directing alkyl substituents of the chiral ligand (*S,S,S*)-**100a** are distal to the titanium atom and directed away from the titanium coordination site, thus having a limited chiral influence on the coordination sphere.[82] It should be noted that the conformation of the monomeric complexes **107a-c** are effectively locked by the lone pair of the apical nitrogen donating its electron density to the central titanium atom, which is also responsible for the preferential formation of the monomeric species.

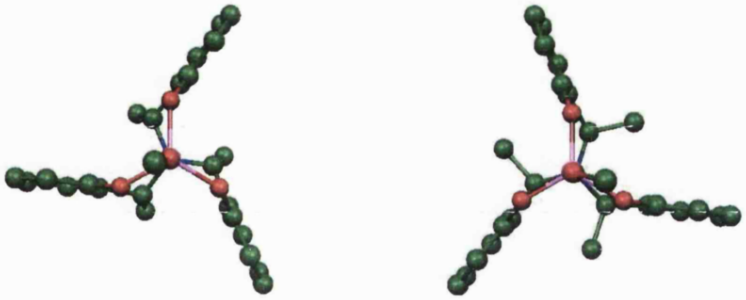
## 2.3 Novel $C_3$-Symmetric Amine Tris(phenolate) Ligands

It was therefore proposed that amine tris(phenolate) ligands (*R,R,R*)-**185**, which combine the use of an apical nitrogen with a sterically demanding tris(phenolate) system should result in chiral metal complexes which have a locked propeller-like conformation (Scheme 66). Furthermore, on complexation, the *ortho*-substituents on the phenolate rings would be directed towards the metal centre, thus effectively relaying stereochemical information to create a chiral environment within the coordination sphere of the metal centre.




**Scheme 66** *Proposed formation of $C_3$-symmetric complex (S,S,S)-**186***

Molecular modelling studies[1] performed on ligand (*R,R,R*)-**185** (where R = H, $R^1$ = Me) complexed to a trigonal bipyramidal transition metal centre *via* its phenolate oxygen atoms. This revealed a $C_3$-symmetric complex (*R,R,R*)-**186** (Scheme 66) which exists as two conformers (Figure 68).



Conformer **A**
Pseudo-axial

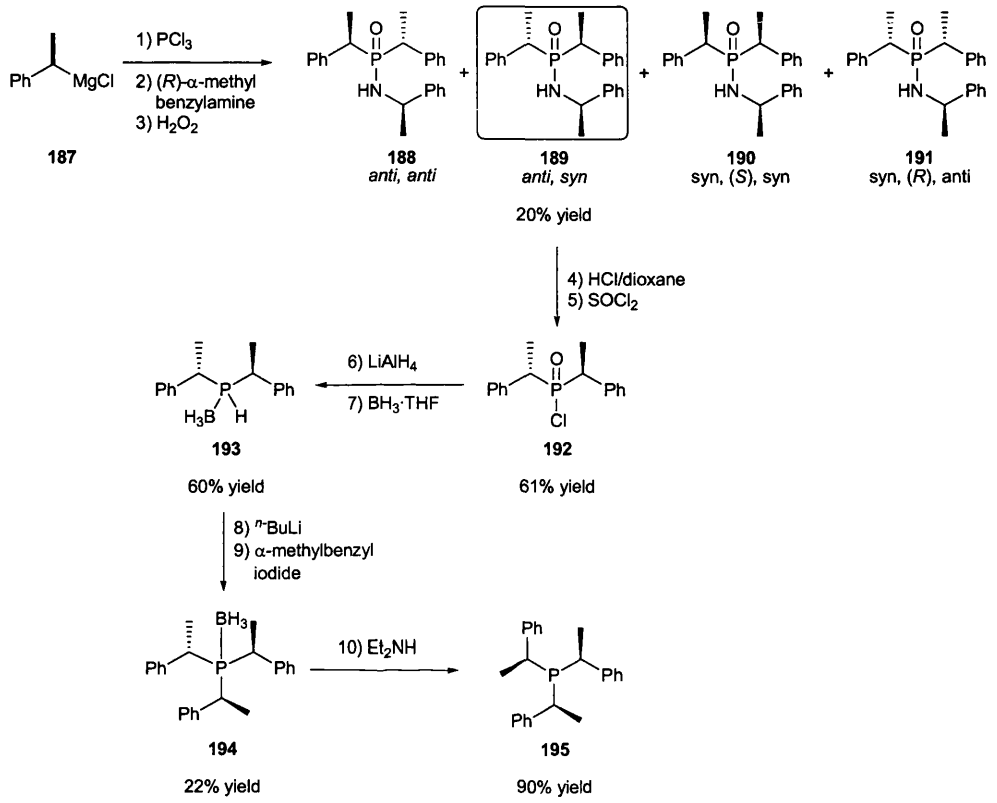
Conformer **B**
Pseudo-equatorial

**Figure 68** *Molecular modelling studies on ligand (R,R,R)-**185** complexed to a trigonal bi-pyramidal transition state metal*

The lowest energy conformer **A** was shown to have the three groups at the stereogenic benzylic positions occupying a *pseudo*-axial environment and the pyramidalised $sp^3$ nitrogen atom datively coordinated to the metal centre. Examination of the structure of **A**, as viewed along the metal-nitrogen axis, revealed that torsional interactions were responsible for the three aryl groups of the ligand adopting a rigid propeller conformation with *M*-symmetry (Figure 68). This results in all three aryl *ortho* substituents being presented towards the metal centre. Therefore the complex can be expected to adopt a conformation which is predisposed to efficiently relay chiral information from the stereogenic centres of the ligand to the coordination sphere of the metal centre. For the alternative conformer **B**, the benzylic methyl groups occupy a *pseudo*-equatorial position and the aryl groups adopt the opposite propeller conformation (*P*-symmetry). Importantly, this conformer was shown to be 38 $kJmol^{-1}$ higher in energy than conformer **A**, and consequently is unlikely to be populated (Figure 68). This means that the energy required to interconvert conformers **A** and **B** *via* inversion of the propeller chirality is prohibitively high, and that complexation of ligand (*R,R,R*)-**185** to a transition metal such as titanium should afford a conformationally locked 'propeller like' metal-ligand complex (*R,R,R*)-**186** in very high de.

[1] Molecular modelling was carried out using polarised split valence basis set MO calculations (6-31G*)

Consideration of the $C_3$-symmetric nature of ligand (*R,R,R*)-**185** revealed that its preparation would require the stereoselective formation of three stereogenic centres, which would necessitate a lengthy multi-step procedure. An example of the type of synthetic protocol that would be required, has been developed by Wyatt *et al.* for the preparation of enantiomerically pure (*R,R,R*)-tris(α-methylbenzyl)phosphane **195** (Scheme 67).[118]



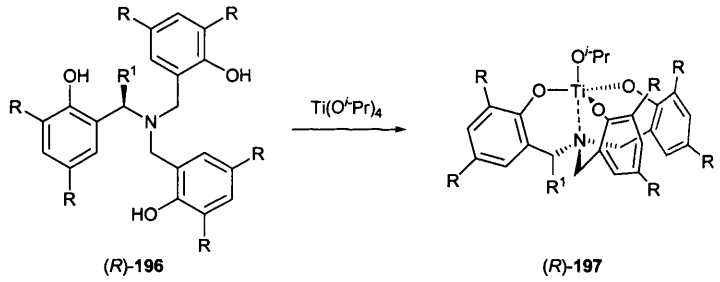

**Scheme 67** *Synthesis of enantiomerically pure (R,R,R)-tris(α-methylbenzyl)phosphane* ***195***

Phosphane **195** was synthesised over ten steps in an overall yield of 1%. Two equivalents of α-methylbenzyl magnesium chloride were reacted with phosphorus trichloride, followed by (*R*)-α-methylbenzylamine and hydrogen peroxide, resulting in all four diastereomers of the phosphonic amides **188-191**. The desired *anti,syn*-diastereomer **189** was separated and hydrolysed and transformed into the phosphonic chloride **192** in an overall yield of 61%. This was then reduced with lithium aluminium hydride and reacted with borane followed by α-methylbenzyl iodide, resulting in borane complex **194** in an overall 22% yield. Finally reaction with diethylamine afforded $C_3$-symmetric phosphane **195** in 90% yield. However, it should be noted that there are

currently no reports on the incorporation of this ligand into a metal complex, or any reports of its use for asymmetric catalysis.

## 2.4 *Pseudo-C*$_3$-Symmetric Complexes

Syntheses of this type are obviously unsuitable for the preparation of a ligand, where an efficient and succinct procedure would be preferable. Indeed, precendent teaches us that in order for a ligand to be widely used, it should be available in as few steps as possible, and preferably less than five. Consequently, it was reasoned that a single stereogenic centre on one of the benzylic positions of the ligand (*R*)-**196** (Scheme 68), would serve equally well to control the propeller chirality of a metal derived complex. It was envisaged that the enantiopure ligand (*R*)-**196**, would afford a *pseudo*-$C_3$-symmetric titanium complex (*R*)-**197**, which would have an essentially identical stereochemical architecture to that of the truly $C_3$-symmetric titanium complex (*R,R,R*)-**186**. Also, if the $R^1$ substituent was sufficiently large, it should exclusively adopt a *pseudo*-axial conformation, resulting in an enantiopure complex in diastereomerically pure form.




**Scheme 68** *Proposed formation of peusdo-C*$_3$*-symmetric complex (R)-**197***

Thus, molecular modelling studies were undertaken on ligand (*R*)-**196** (R = H, $R^1$ = Me) complexed to a trigonal bi-pyramidal transition metal. As expected, this revealed a *pseudo*-$C_3$-symmetric complex (*R*)-**197** (Scheme 68) and it was shown that once again the lower energy conformer **A** occurred in which the group at the lone stereogenic benzylic position occupied a *pseudo*-axial environment and the pyramidalised $sp^3$ nitrogen atom was datively coordinated to the metal centre (Figure 69).


**Figure 69** *Molecular modelling studies on ligand (R)-**196** complexed to a trigonal bi-pyramidal transition state metal*

Examination of the structure of **A**, as viewed along the metal-nitrogen axis, revealed that it adopted a rigid propeller conformation with *M*-symmetry, in the same manner as (*R,R,R*)-**186**. The corresponding conformer **B**, in which the benzylic methyl group occupied a *pseudo*-equatorial position and the aryl groups adopt an opposite propeller conformation (*P*-symmetry), was shown to be 14 $kJmol^{-1}$ higher in energy than conformer **A** (Figure 69). Despite this energy difference being smaller than that previously observed for the truly $C_3$-symmetric complex, the energy difference is still sufficiently large to ensure that conformer **B** will be largely unpopulated. The use of a larger R group ($^{i}$Pr, $^{t}$Bu) would also increase this energy difference and inter-conversion would become even more unfavoured due to steric considerations.

Though the energy difference between the two conformers of complex (*R*)-**197** is lower than that of complex (*R,R,R*)-**186**, these modelling studies have clearly demonstrated that the use of only one stereogenic centre in the ligand should be sufficient to fix the propeller chirality of the complex.

### 2.4.1 Literature Precedence

An extensive review of the literature revealed that the use of a single stereogenic centre to dictate the propeller-type chirality of metal complexes has been demonstrated previously by Canary *et al.*[119,120] In 1998, a consolidation of previous work was published, in which the structures of the racemic zinc complexes of amines **198a,b** and **199** were reported (Figure 70).[120] When a racemic mixture of amine **198a** was complexed to zinc, it was found that the zinc(II) cation in the resulting racemic complex was penta-coordinate in a distorted trigonal bipyramidal environment. The pyridyl nitrogens occupied the equatorial positions and the apical amine nitrogen was shown to adopt an axial position. It was also shown that for the (*R*)-enantiomer of the amine, the

benzylic methyl substituent occupied the lower energy *pseudo*-axial environment with the three pyridine rings forming a propeller with exclusively *M*-symmetry. Conversely, (*S*)-**198a** resulted in the complex with *P*-symmetry. This was also found to be the case for the zinc complexes of amines **198b** and **199**. The methyl groups in ligands **198a** and **199** were found to be large enough to lock the propeller conformation, as no inter-conversion between the *M*- and *P*-enantiomers was observed. However, to date these complexes have not been applied as catalysts for asymmetric transformations.

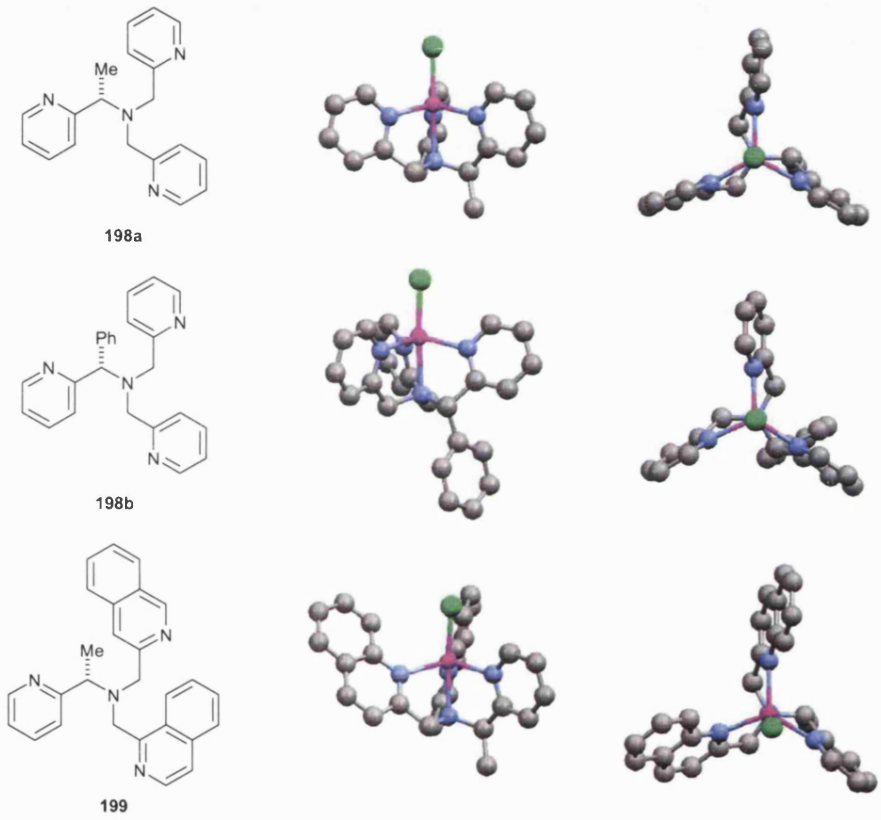
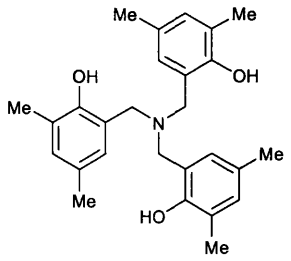



**Figure 70** *Side and top views of the X-ray crystal structures of racemic pseudo-$C_3$-symmetric zinc complexes of amines **198a,b** and **199** (only one of two similar molecules found within the asymmetric unit is shown and hydrogens are omitted for clarity).*

## 2.5 Synthesis and Screening of a Racemic Amine Tris(phenolate) Complex

Before beginning the synthesis of ligand (*S*)-**196** it was thought necessary to examine the Lewis acid activity of the $C_3$-symmetric complex of achiral ligand **200** (Figure 71). This was to ensure that the apical nitrogen-metal bond, which is crucial in locking the propeller chirality of the ligand, did not have any detrimental effect on the activity of the complex since donation of the nitrogen lone pair to the metal atom is likely to

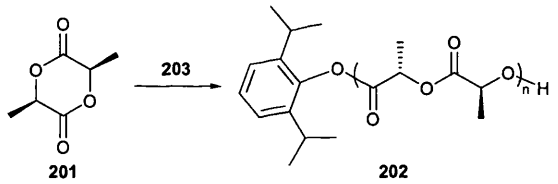
reduce the Lewis acidity of the complex by increasing the electron density of the metal centre.




**200**

**Figure 71** *Achiral amine tris(phenolate) ligand* ***200***

Various metal complexes of ligand **200** and its derivatives are known and a range of these are depicted in Figure 72.[61,121-123] Interestingly, some of these complexes have been found not to be $C_3$-symmetric, which illustrates the importance of the choice of metal. The Lewis acidity of some of these complexes has been demonstrated. For example, whilst tantalum complex **203** (Figure 72b) failed to catalyse the polymerisation of lactides,[121] treatment of racemic lactide (*rac*)-**201** with titanium complex **204** (Figure 72c) at 130 °C for 24 hours resulted in polylactide **202** in a 68% yield with a polydiversity index (PDI) of 1.43 (Scheme 69, Table 38, entry 1).[122] Chiral lactide (*R,R*)-**201** was also employed, resulting in polylactide **202** in 69% yield with a PDI of 1.51 (Table 38, entry 2). Interestingly, the di-*iso*-propylphenolate ligand of the catalyst was found to be attached to the resulting polymer.




**201** **202**

**Scheme 69** *Polymerisation of lactide* ***201***

**Table 38**

| Entry | Lactide | g polymer | Yield /% | $M_w$[a] | $M_n$[b] | PDI[c] |
|---|---|---|---|---|---|---|
| 1 | (*rac*)-**201** | 1.35 | 68 | 23 000 | 16 000 | 1.43 |
| 2 | (*R,R*)-**201** | 1.36 | 69 | 29 300 | 19 400 | 1.51 |

[a] The weight average molecular weight; [b] The number average molecular weight; [c] PDI = $M_w/M_n$

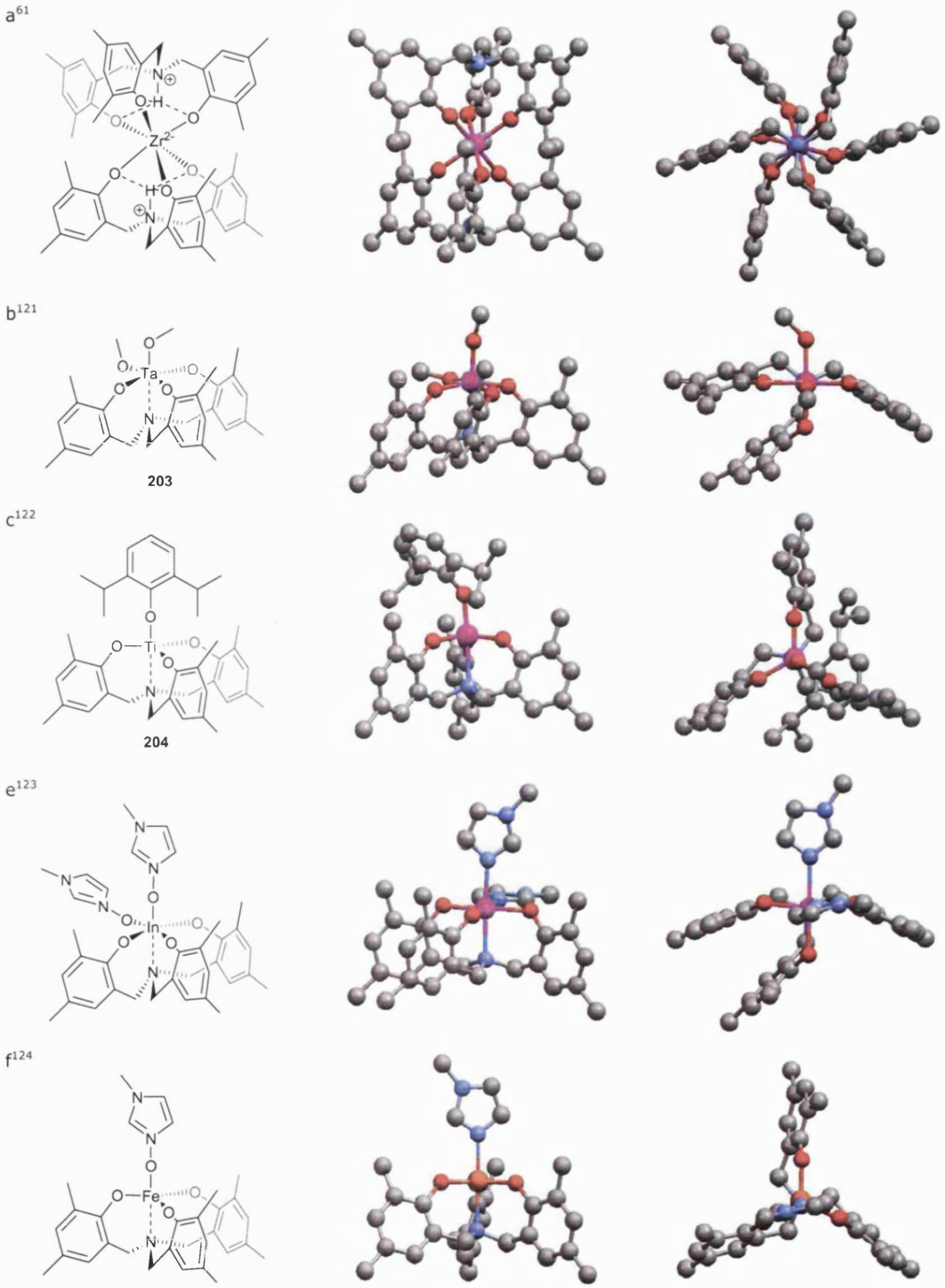
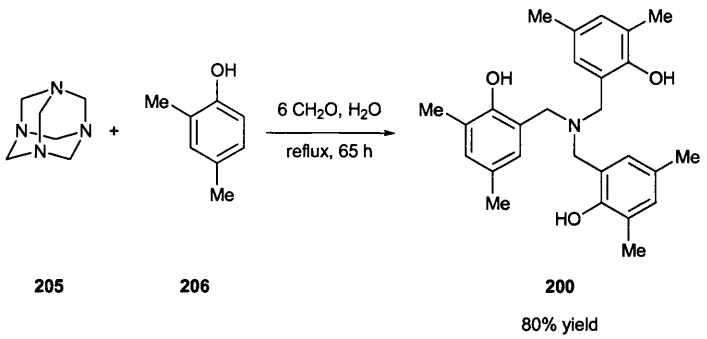



**Figure 72** *Side and top views (respectively) of metal complexes of* ***200***

Given the activity of these types of titanium complexes as a polymerisation catalyst, it was considered that the titanium complex of tris(2-hydroxy-3,5-dimethylbenzyl) amine **200** should therefore be a versatile catalyst for organic synthesis.

### 2.5.1 Synthesis of Tris(2-hydroxy-3,5-dimethylbenzyl) Amine 200

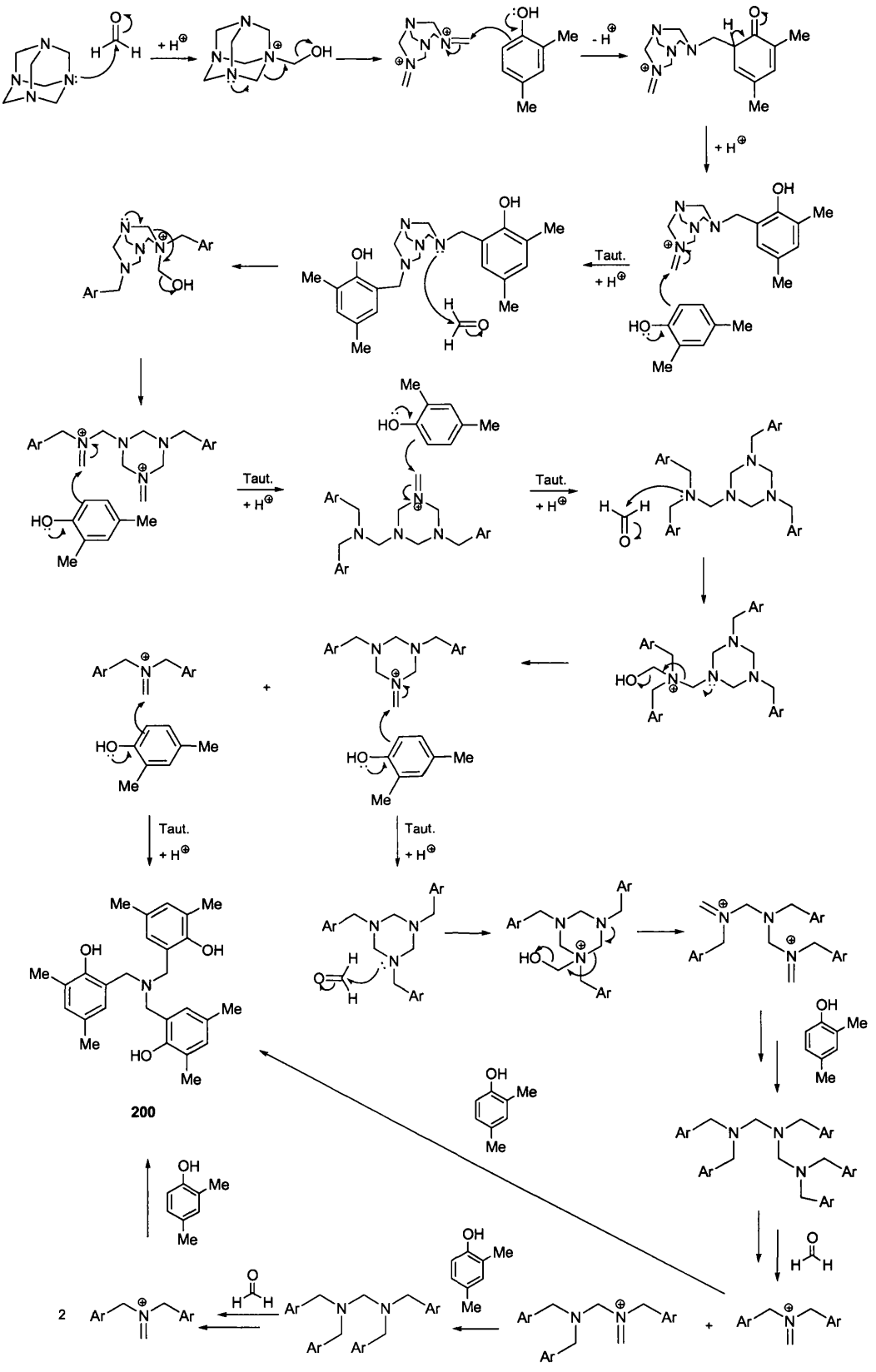
Ligand **200** was prepared *via* a one-pot variant of the Mannich reaction; hexamethylene tetramine **205**, 2,4-dimethylphenol **206**, and *para*-formaldehyde were refluxed in water for 64 hours. After this time the resulting yellow precipitate was filtered and washed with cold hexane to afford amine **200** as an off-white solid in 80% yield (Scheme 70).




**Scheme 70** *One-pot synthesis of achiral ligand* ***200***

The structure of tris(2-hydroxy-3,5-dimethylbenzyl) amine **200** was evidenced by the $^1$H NMR spectrum, which revealed two signals at $\delta$ = 2.20 and 2.21 ppm corresponding to the 18 protons of the three sets of both aryl methyl groups. A resonance at $\delta$ = 3.63 ppm indicated the presence of six equivalent benzylic protons. The ion detected in the high resolution mass spectroscopy appeared at 420.2531 (where $[M-H]^+$ – $C_{27}H_{33}NO_3$ requires 420.2533), thus confirming the structure of the tris(phenol) ligand.

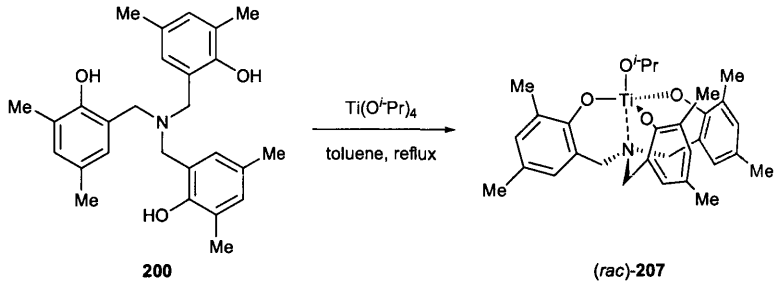
The mechanism of the formation of amine **200** has not been discussed in the literature previously, but one possible mechanism is shown in Scheme 71. It is proposed that hexamethylene tetramine attacks the carbonyl of *para*-formaldehyde to form an α-alcohol aminol ion which then eliminates to form an iminium species. 2,4-Dimethylphenol then adds to the iminium ion followed by tautomerisation, resulting in a mono-aryl amine. This procedure is then repeated a total of five times to afford three equivalents of ligand **200**.




**Scheme 71** *Proposed mechanism of the formation of achiral ligand* ***200***

### 2.5.2 Synthesis of Amine Tris(phenolate) Titanium *iso*-Propoxide (*rac*)-207

Amine tris(phenolate) titanium *iso*-propoxide (*rac*)-**207** was then prepared in high yield (88%) from ligand **200** using a modification of the procedure reported by Kol *et al.* (Scheme 72).[125] Titanium tetra *iso*-propoxide and **200** were heated to reflux in toluene and the solvent removed to yield titanium complex (*rac*)-**207** as a yellow powder.




200 (*rac*)-207

**Scheme 72** *Preparation of amine tris(phenolate) titanium iso-propoxide complex (rac)-**207***

Its identity was established spectroscopically, with the *iso*-propoxide ligand showing a doublet at $\delta$ = 2.15 ppm and a heptet at $\delta$ = 5.13 ppm in the $^1$H NMR spectrum. The signals corresponding to the aryl methyl groups also shifted upfield to $\delta$ = 2.14 and 2.17 ppm, when compared to the uncomplexed ligand ($\delta$ = 2.20 and 2.21 ppm). The $^1$H NMR spectrum also revealed two broad doublets at $\delta$ = 2.75 and 3.89 ppm ($J$ = 10.6 Hz), which were ascribed to the diastereotopic benzylic protons of the tripodal ligand. Elemental analysis showed that the composition of the complex was as follows: C, 68.8%; H, 7.1%; N, 2.7% ($C_{30}H_{37}NO_4Ti$ requires C, 68.5; H, 7.1; N, 2.6%).

The structure was confirmed by a single crystal X-ray structure (Figure 73).[126] This revealed that the complex was a monomeric, $C_3$-symmetric complex as expected, with the trigonal pyramidal titanium centre lying slightly above the plane of the three equatorial phenolate oxygen atoms [distance of Ti atom above the plane of the three phenolate O atoms (Å): 0.251(1)/0.247(1)]. The bonds between the titanium atom and the phenolate oxygen atoms are of very similar lengths, showing that the titanium is in a symmetrical environment [Ti-O(phenolate) distances (Å): Ti-O(1) 1.862(2), Ti-O(2) 1.845(2), Ti-O(3) 1.851(2)]. The axial sites are occupied by the apical nitrogen and the monodentate *iso*-propoxide anion. The Ti-N bond length is 2.303(2) Å, whilst the Ti-O$^i$Pr distance is 1.774(2) Å.

Although ligand **200** is achiral, the complex that is formed is racemic, since complexation to the metal centre results in the formation of two enantiomers with

differing propeller-type chirality. This was evident by the presence of both the *M*- and *P*-enantiomers in the crystallographic asymmetric unit.

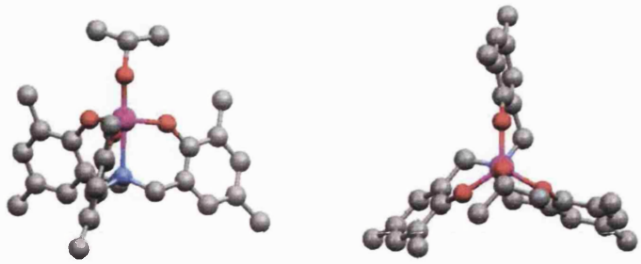


**Figure 73** *Side and top views (left and right respectively) of the X-ray crystal structure of amine tris(phenolate) titanium iso-propoxide complex (rac)-**207** (only one of two similar molecules found within the asymmetric unit is shown and hydrogens are omitted for clarity).*

### 2.5.3 Catalytic Screening of *iso*-Propoxide Complex (*rac*)-207

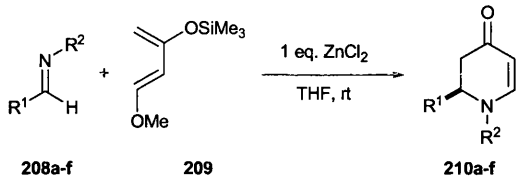
Having prepared monomeric complex (*rac*)-**207**, our next goal was to demonstrate its potential as a Lewis acid for organic synthesis. In this regard, it was decided to screen its activity as a Lewis acid catalyst for the *aza*-Diels Alder reaction. Consequently, a brief review of aspects of this reaction is now described.

#### Literature Precedence

Despite the great achievements concerning enantioselective *hetero*-Diels Alder reactions of carbonyl compounds, there has been less advancements for the analogous asymmetric reaction of imines.[127] This is due to the following problems which are commonly encountered when attempting Lewis acid catalysed reactions with imines:

1. The nitrogen atom of an imine is more Lewis basic than its carbonyl counterpart, and as such the coordination of the imine (or the product) to the Lewis acid catalyst is stronger. This can lead to deactivation of the catalyst, meaning that stoichiometric quantities of often expensive catalysts are required for the reaction to achieve high conversion.
2. Imines are commonly formed as a mixture of E and Z isomers.
3. The double bonds of imines are less reactive towards nucleophiles than carbonyl groups, whilst also being poor electrophiles.
4. Enolisable imines tend to form enamines.
5. Some imines are unstable, which can lead to difficulties in their preparation and use.

The first *aza*-Diels Alder reaction was reported in 1982 by Danishefsky *et al.* which was catalysed by zinc(II) chloride.[128] Reaction of a range of imines **208a-f** with 1.1 equivalents of Danishefsky's diene **209** resulted in the products in moderate yields (33-53%) (Scheme 73, Table 39). It was found that increasing the equivalents of diene resulted in much higher yields of dihydropyridinone products **210a-f** (47-76%).



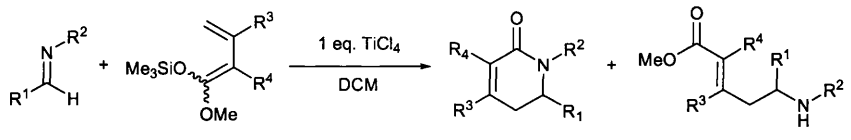

**208a-f** **209** **210a-f**

**Scheme 73** *The first aza-Diels Alder reported by Danishefsky et al.*[128]

**Table 39**

| Product | $R^1$ | $R^2$ | Equivalents of diene | Yield /% |
|---|---|---|---|---|
| **210a** | Ph | Ph | 1.1<br>4.3 | 48<br>62 |
| **210b** | $^{i}$Pr | Bn | 1.1<br>3.8 | 44<br>69 |
| **210c** | $(CH_2)_2Me$ | $(CH_2)_3Me$ | 1.1<br>3.1 | 49<br>68 |
| **210d** | Ph | $CH_2CH(OMe)_2$ | 1.1<br>4.2 | 53<br>76 |
| **210e** | C(Me)$CHCH_2Me$ | Bn | 1.1<br>2.3 | 33<br>47 |
| **210f** | CHCHPh | Ph | 1.1<br>4.6 | 41<br>72 |

It was later reported that titanium(IV) chloride was also an efficient catalyst for this type of reaction.[129] Brandstadter *et al.* noted that treatment of a range of imines **211a-c** with titanium(IV) chloride followed by diene **212** resulted in a mixture of the corresponding 5,6-dihydro-2-pyridones **213a-i** and 5-amino-2-alkenoates **214a-i** (Scheme 74, Table 40).




**211a-c** **212a-c** **213a-i** **214a-i**

**Scheme 74** *Reaction of imines **211a-c** with ketene silyl acetals **212a-c** catalysed by $TiCl_4$*

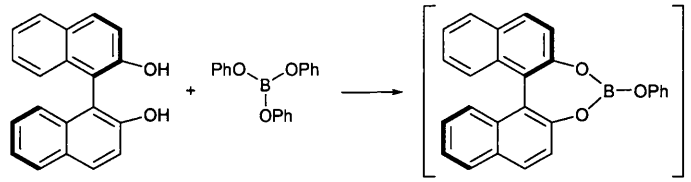
**Table 40**

| Entry | Products | $R^1$ | $R^2$ | $R^3$ | $R^4$ | 213 Yield[a] /% | 214 Yield[a] /% | Conversion[b] /% |
|---|---|---|---|---|---|---|---|---|
| 1 | **a** | $^i$Pr | Bn | H | H | 53 (41) | 9 (-) | 99 |
| 2 | **b** | Ph | Bn | H | H | 20 (10) | 78 (77) | 98 |
| 3 | **c** | Ph | Ph | H | H | 0 | 32 (23) | 98 |
| 4 | **d** | $^i$Pr | Bn | Me | H | 96 (73) | 4 (-) | 100 |
| 5 | **e** | Ph | Bn | Me | H | 92 (85) | 0 | 92 |
| 6 | **f** | Ph | Ph | Me | H | 38 (34) | 62 (40) | 100 |
| 7 | **g** | $^i$Pr | Bn | H | Me | 38 (27) | 43 (41) | 94 |
| 8 | **h** | Ph | Bn | H | Me | 0 | 94 (79) | 96 |
| 9 | **i** | Ph | Ph | H | Me | 0 | 98(89) | 98 |

[a] Yield determined by GLC (Isolated Yield); [b] Conversion based on the imine consumed

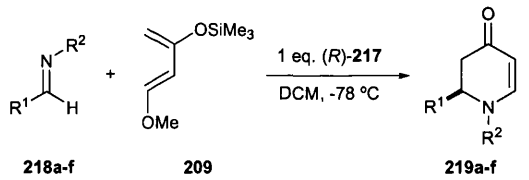
The ratio of 5,6-dihydro-2-pyridones **213a-i** to 5-amino-2-alkenoates **213a-i** was found to be dependant on the substitution patterns of both the diene and the dienophile. For example, the introduction of a methyl group at the 3-position of the diene (**212b**: $R^3$ = Me) afforded predominantly dihydropyridinones **213d-f** in moderate to good isolated yields (34-85%) (Table 40, entries 4-6). However, the introduction of a methyl group at the 2-position of the diene (**212c**: $R^4$ = Me) resulted in exclusive formation of the acyclic 5-amino-2-alkenoates **214a-i** in good isolated yields (41-89%) (Table 40, entries 7-9). The isolation of acyclic 5-amino-2-alkenoates **214a-i** points to the reaction proceeding *via* a stepwise rather than a concerted mechanism (*vide infra*).

In 1993 Yamamoto *et al.* reported that one equivalent of catalyst (*R*)-**217** generated *in situ* from (*R*)-BINOL **215** and triphenyl borate **216** (Scheme 75), catalysed *aza*-Diels Alder reactions between a range of imines and Danishefsky's diene, resulting in the products **219a-e** in 4-85% ee and 13-89% yield, after 5 hours (Scheme 76, Table 41).[130]




(*R*)-**215** **216** (*R*)-**217**

**Scheme 75** *Generation of catalyst (R)-**217** in situ*




218a-f 209 219a-f

**Scheme 76** *Aza-Diels Alder reaction catalysed by (R)-**217***

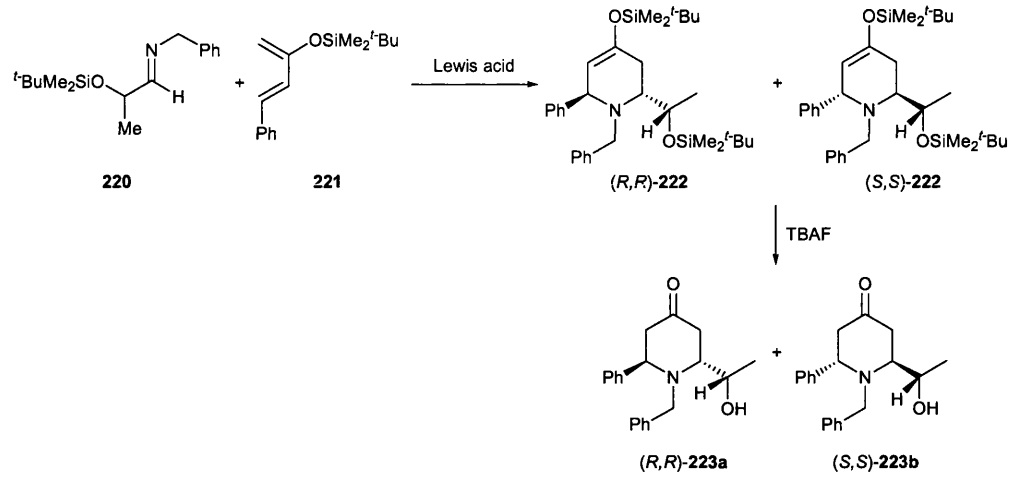
**Table 41**

| Entry | Product | $R^1$ | $R^2$ | Yield /% | ee /% |
|---|---|---|---|---|---|
| 1 | **219a** | Ph | Bn | 75 | 82 |
| 2 | **219b** | 2-naphthyl | Bn | 83 | 84 |
| 3 | **219c** | 3,5-$(MeO)_2(C_6H_3)$ | Bn | 89 | 74 |
| 4 | **219d** | $^{c}$hexyl | Bn | 45 | 76 |
| 5 | **219e** | Ph | $^{i}$Pr | 13 | 4 |
| 6 | **219f** | Ph | 3,4-$(MeO)_2(C_6H_3)$ | 73 | 85 |

The catalytic activity of (*R*)-**217** was compared to other Lewis acid catalysts for the reaction between benzyl-phenylmethylene-amine **218a** and Danishefsky's diene **209**. It was found that $TiCl_2(O^iPr)_2$, performed poorly in this reaction, yielding *N*-benzyl-2,3-dihydro-2-phenyl-1H-pyridin-4-one **219a** in only 20% yield and 17% ee, an observation that proved important in relation to the research described herein.

In 1997 Akiba *et al.* reported the *aza*-Diels Alder reaction of α-silyloxy imine **220** with activated 2-silyloxy-1,3-diene **221** (Scheme 77).[131] A series of Lewis acids were screened as catalysts for this reaction and the optimised results are shown in Table 42. It was found that only two out of four possible diastereomers were observed in all of these reactions. Trimethylsilyl triflate had previously been reported by the authors as an efficient catalyst for this reaction.[132] Optimisation of the conditions for its use resulted in the piperidinone products (*S,S*)-**223a** and (*R,R*)-**223b** in a ratio of 77:23 and 97% yield after 72 hours (Table 42, entry 1). Reaction of α-silyloxy imine **220** with activated 2-silyloxy-1,3-diene **221** in $^{n}$hexane in the presence of zinc(II) triflate resulted in (2*R*,6*R*)-1-benzyl-2-((*S*)-1-hydroxyethyl)-6-phenylpiperidin-4-one **223a** as the major product in a diastereomeric ratio of 89:11 and a yield of 93%, after 48 hours (Table 42, entry 2). It was found that while titanium(IV) *iso*-propoxide did not catalyse this reaction, titanium(IV) chloride was a very efficient catalyst affording (2*S*,6*S*)-1-benzyl-2-((*S*)-1-hydroxyethyl)-6-phenylpiperidin-4-one **223b** as the major diastereomer in a ratio of <2:98 (**223a**:**223b**) (Table 42, entries 3 and 4). Therefore, the use of titanium(IV) chloride resulted in the opposite diastereomer as the major product when

compared to the other Lewis acids. However, when the reaction was performed in $^{n}$-hexane, the selectivity was reversed, although the yield of the reaction was very poor (12%) (Table 42, entry 5).




**Scheme 77** *Aza-Diels Alder between α-silyloxy imine **220** and activated 2-silyloxy-1,3-diene **221***

**Table 42**

| Entry | Lewis Acid | Solvent | Time /h | 223a : 223b | Yield /% |
|---|---|---|---|---|---|
| 1 | TMSOTf | toluene | 72 | 77 : 23 | 97 |
| 2 | $Zn(OTf)_2$ | $^{n}$-hexane | 48 | 89 : 11 | 93 |
| 3 | $Ti(O^{i}Pr)_4$ | DCM | 168 | - | - |
| 4 | $TiCl_4$ | $^{i}$-PrCN | 24 | <2 : 98 | 87 |
| 5 | $TiCl_4$ | $^{n}$-hexane | 24 | 98 : <2 | 12 |

The contrasting selectivity that was observed when titanium(IV) chloride was used as the catalyst, when compared to the other Lewis acids, is ascribed to the chelation behaviour of the complexes (Figure 74). It was proposed that in the presence of zinc(II) triflate, the Felkin-Ahn model was obeyed, resulting in piperidinone **223a**; whereas titanium(IV) chloride was chelated by the imine, thus affording piperidinone **223b**.

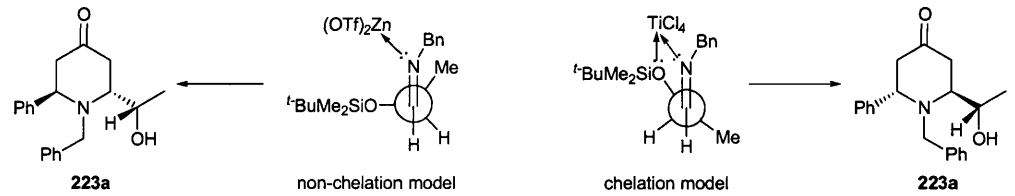
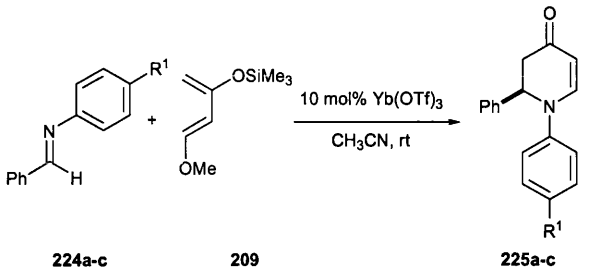



**Figure 74** *Non-chelation and chelation models (left and right respectively) proposed by Akiba et al.[132] to explain the opposite diastereoselectivity for $Zn(OTf)_2$ and $TiCl_4$*

In 1995, Kobayashi *et al.* reported the catalysis of *aza*-Diels Alder reactions by lanthanide triflates.[133,134] In particular it was found that ytterbium(III) triflate efficiently catalysed the reaction between Danishefsky's diene **209** and a representative range of imines **224a-c** to yield the corresponding dihydropyridinone derivatives **225a-c** in good yields (82-93%) (Scheme 78, Table 43).



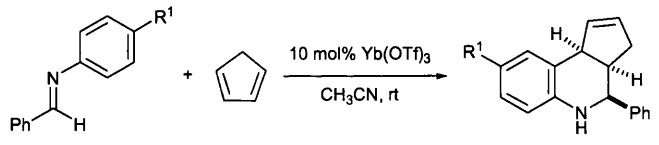

**224a-c** **209** **225a-c**

**Scheme 78** *Aza-Diels Alder catalysed by Yb(OTf)$_3$*

**Table 43**

| Product | $R^1$ | Yield /% |
|---|---|---|
| **225a** | H | 93 |
| **225b** | OMe | 82 |
| **225c** | Cl | 92 |

The reaction of these imines with cyclopentadiene **156** under the same conditions was also examined and it was found that the reaction course changed, resulting in the imine acting as an *aza*-diene towards one of the double bonds in cyclopentadiene. This afforded the corresponding tetrahydroquinolines **226a-c** in good yields (38-85%) (Scheme 79, Table 44).



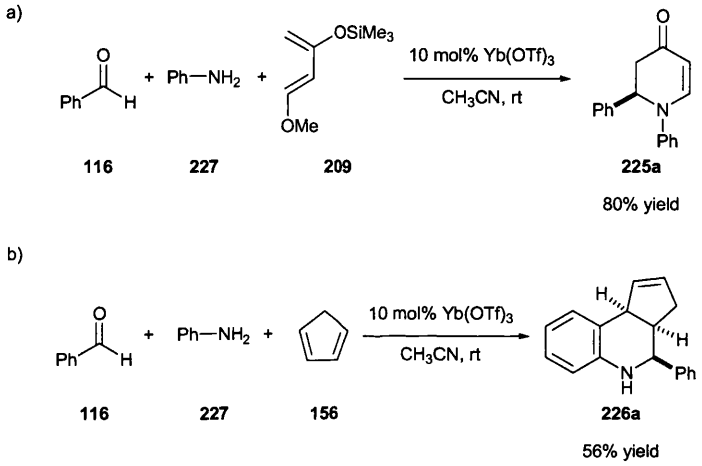

**224a-c** **156** **226a-c**

**Scheme 79** *Aza-Diels Alder catalysed by Yb(OTf)$_3$*

**Table 44**

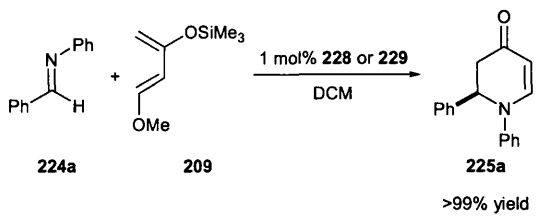
| Product | $R^1$ | Yield /% |
|---|---|---|
| **226a** | H | 85 |
| **226b** | OMe | 38 |
| **226c** | Cl | 85 |

This work was also extended to include the one-pot, three-component coupling of aldehydes, amines and dienes to yield the corresponding dihydropyridinone or tetrahydroquinoline in good yields. For example, reaction of benzaldehyde **116**, aniline **227**, and Danishefsky's diene **209** in the presence of 10 mol% ytterbium(III) triflate and magnesium sulphate, resulted in the formation of 1,2-diphenyl-2,3-dihydropyridin-4(1H)-one **225a** in 80% yield (Scheme 80a). The reaction of benzaldehyde **116**, aniline **227**, and cyclopentadiene **156** under the same conditions afforded 4-phenyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[*c*]quinoline **226a** in 56% (Scheme 80b). In 1998, Creswell *et al.* reported the use of a polymer-supported quenching methodology for the parallel purification of the products of these reactions.[135]



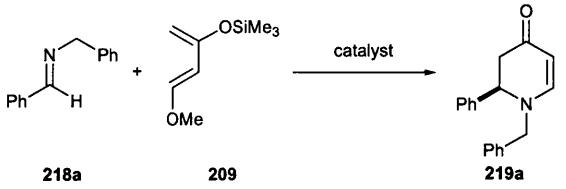

**Scheme 80** *One-pot, three-component coupling reactions catalysed by $Yb(OTf)_3$*

Frost and Weller *et al.* have described the use of two silver(I)–phosphine complexes containing $[CB_{11}H_{12}]_2$ (**228**) and $[CB_{11}H_6Br_6]_2$ (**229**) for the *aza*-Diels Alder reaction.[136] These complexes catalysed the *aza*-Diels Alder reaction between *N*-benzylidenephenylamine **224a** and Danishefsky's diene **209**, resulting in 1,2-diphenyl-2,3-dihydropyridin-4(1H)-one **225a** in >99% yield after 2 hours (Scheme 81).




**Scheme 81** *Aza-Diels Alder between N-benzylidenebenzenamine **224a** and Danishefsky's diene **209** catalysed by silver(I)-phosphine complexes **228** and **229***

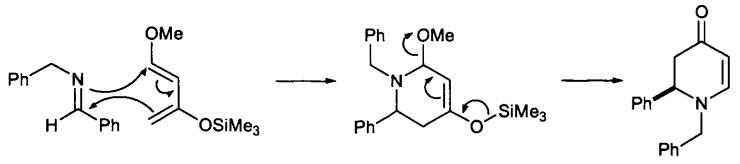
Given that there were few examples of titanium complexes catalysing *aza*-Diels Alder reactions in the literature, it was decided to screen $C_3$-symmetric complex (*rac*)-**207** for catalytic activity in the *aza*-Diels Alder between benzyl-phenylmethylene-amine **218a** and Danishefsky's diene **209** (Scheme 82) in DCM, since this reaction was known not to occur without a catalyst.[136] There are also no examples, to date, of enantioselective *aza*-Diels Alder reactions being catalysed by chiral titanium complexes, thus it was hoped that a chiral $C_3$-symmetric complex would induce high enantioselectivity into this type of reaction.




**Scheme 82** *Aza-Diels Alder reaction*

### Mechanism of the *Aza*-Diels Alder Reaction

The *aza*-Diels Alder reaction can proceed *via* two possible mechanisms. The first is the pericyclic cycloaddition Diels Alder reaction, which is a concerted mechanism in which all the bonds are broken and made synchronously (Scheme 83). The observed pyridinone product results from the elimination of TMSOMe from the six-membered cycloaddition product.




**Scheme 83** *The concerted mechanism of the aza-Diels Alder reaction*

In order to understand the regiochemistry of the reaction, the HOMO and LUMO of the system need to be considered. It is usual to consider the HOMO of the diene and the LUMO of the dienophile due to their being respectively electron rich and electron deficient. The regioselectivity of the reaction is controlled by the orbital coefficients of the LUMO and HOMO of the system, with the best interaction being between the reactants bearing large coefficients, which after elimination of TMSOMe results in the observed pyridinone (Figure 75).

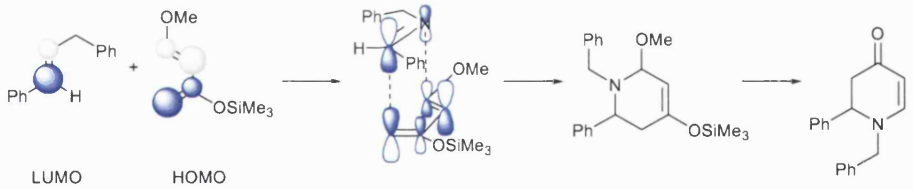



**Figure 75** *Representation of the orbital coefficients of the aza-Diels Alder reaction and their interaction*

The stereochemistry of the reaction is controlled by the orbital overlap. The dienophile can approach the diene in two different orientations, either *endo*- or *exo*-, which results in two diastereomers of the six-membered adduct and affords two enantiomers of the pyridinone. Although the *endo*-transition state is more hindered, it is stabilised by secondary overlap of the *p*-orbital of the oxygen and the π-system of the phenyl ring (Figure 76). The *exo*- transition state, however, is not stabilised by any secondary overlap, but it is less hindered meaning that it is thermodynamically more stable.

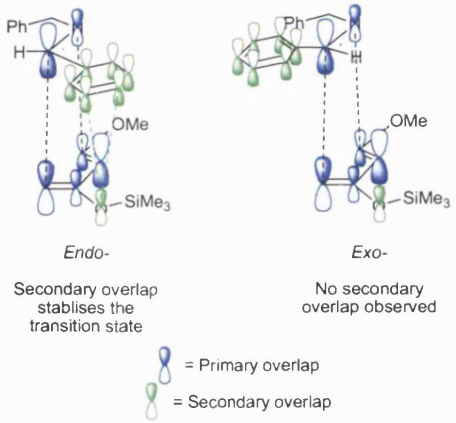
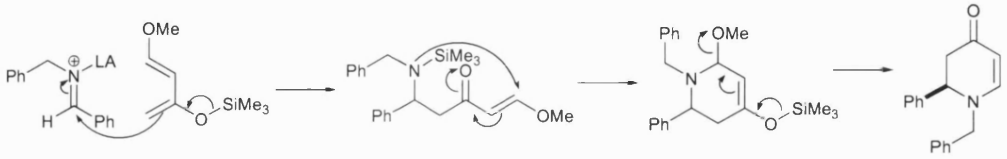



**Figure 76** *Primary and secondary overlap in the endo- and exo- transition states of the aza-Diels Alder reaction*

The second possible mechanism is a stepwise process, which proceeds *via* a Mannich-type reaction, followed by a conjugate addition (Scheme 84). It has been proven that under certain conditions hetero-Diels Alder reactions proceed *via* this stepwise mechanism rather than the concerted mechanism described above.[137]




**Scheme 84** *Stepwise Mannich-type mechanism*

The addition of a Lewis acid promotes the reaction by decreasing the LUMO and HOMO energies of the dienophile, leading to improved interactions with the diene, regardless of the reaction pathway. This is due to the energy difference between the $HOMO_{diene}$ and $LUMO_{dienophile}$ being reduced (Figure 77). The addition of a Lewis acid can sometimes influence the pathway of the reaction due to its size and the orientation of its coordination to the imine.

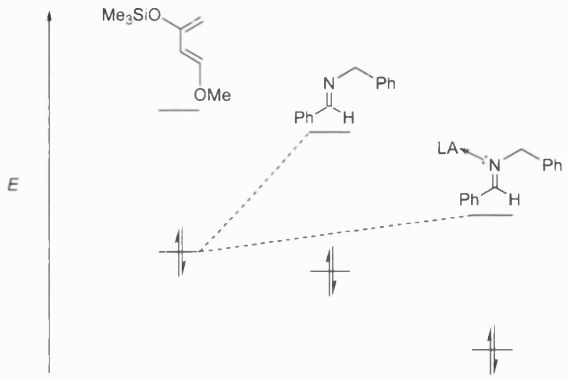
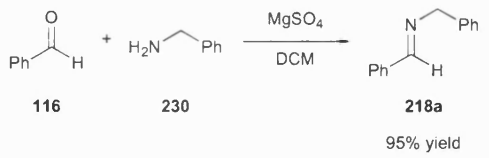



**Figure 77** *An energy level diagram of the $HOMO_{diene}$-$LUMO_{dienophile}$ controlled aza-Diels Alder reaction in the absence and presence of a Lewis acid*

As there are two possible pathways for this reaction, it will be referred to as a formal *aza*-Diels Alder reaction throughout the rest of this thesis.

### Synthesis of Benzyl-phenylmethylene-amine 218a

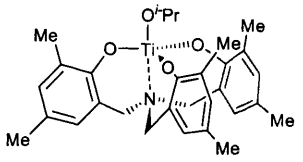
Imine **218a** was formed by treatment of benzaldehyde **116** and benzylamine **230** with magnesium sulphate in DCM, using a modified literature procedure (Scheme 85).[130] This resulted in benzyl-phenylmethylene-amine **218a** in a very good 95% yield, after 4 hours. Its structure was confirmed by the comparison of its $^1$H NMR spectrum with that previously published in the literature.[130] The absence of a peak at $\delta$ = 10.1 ppm corresponding to benzaldehyde and the presence of a signal at 8.44 ppm, provided easy confirmation of imine formation.




**Scheme 85** *Formation of benzyl-phenylmethylene-amine **218a***

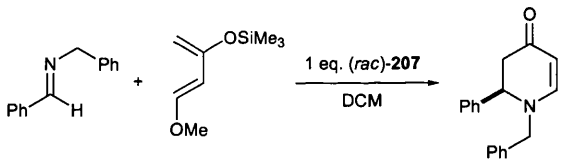
### *Aza*-Diels Alder Reaction Catalysed by (*rac*)-207

Unfortunately, titanium *iso*-propoxide (*rac*)-**207** (Figure 78) was found to be a poor Lewis acid catalyst for the formal *aza*-Diels Alder reaction. For example, addition of one equivalent of complex (*rac*)-**207** to a solution of benzyl-phenylmethylene-amine **218a** and Danishefsky's diene **209** at room temperature, resulted in dihydropyridinone **219a** in 62% conversion (40% isolated yield), after 2 hours (Scheme 86, Table 45, entry 1). The formation of dihydropyridinone **219a** was confirmed by spectroscopic analysis and comparison of the data to literature values.[130] The signals at $\delta = 4.04$ and 4.27 ppm ($J = 15.1$ Hz) which correspond to the two benzylic protons were shown to be an AB-quartet system, which is evident of the diastereotopic nature of the protons. The two protons on C-2 of the ring were also shown to be non-equivalent and diastereotopic, with the resonances being doublets of doublets at $\delta = 2.60$ and 2.77 ppm ($J = 16.5$ Hz).




(*rac*)-**207**

**Figure 78** *Titanium iso-propoxide (rac)-**207***




**218a** **209** **219a**

**Scheme 86** *Aza-Diels Alder reaction catalysed by (rac)-**207***

**Table 45**

| Entry | Catalyst mol% | Time /h | Conversion[a] /% | Yield /% |
|---|---|---|---|---|
| 1 | 100 | 2 | 62 | 40 |
| 2 | 100 | 21 | 72 | 32 |
| 3 | 10 | 48 | 30 | 12 |

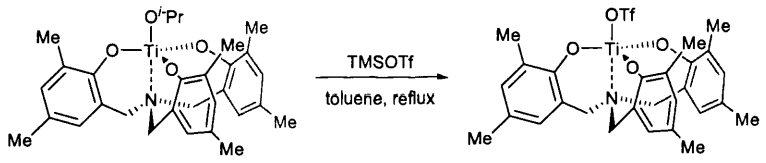
[a] Conversion measured *via* $^1$H NMR spectroscopic analysis

It was found that when the reaction was left for 21 hours the conversion was still only 72%, whilst the isolated yield had decreased to 32%, indicating that the majority of activity occurred in the first two hours (Table 45, entry 2). Whilst this result indicated that the complex was acting as a Lewis acid, it appeared that the reaction was very slow.

It was decided to attempt the reaction with 10 mol% of (*rac*)-**207** to determine whether the complex could also acted as a catalyst at sub-stoichiometric levels. This reaction proceeded to only 30% conversion after 48 hours, resulting in *N*-benzyl-2,3-dihydro-2-phenyl-1H-pyridin-4-one **219a** being formed in 12% isolated yield (Table 45, entry 3). This result was positive however, as it proved that the complex was potentially catalytic, the fact that a long reaction time was required was discouraging, as it implied that the catalyst was not sufficiently active to be useful as a general Lewis acid for organic synthesis.

### 2.5.4 Synthesis of Amine Tris(phenolate) Titanium Triflate (*rac*)-231

It was proposed that the lack of activity of complex (*rac*)-**207** as a Lewis acid was a consequence of additional stabilisation of the metal centre by donation of electron density from the apical nitrogen. It was proposed that replacing the *iso*-propoxide ligand with a more weakly coordinating axial triflate ligand would enhance the reactivity of the catalyst. Therefore, complex (*rac*)-**207** was reacted with trimethylsilyl triflate (TMSOTf) in toluene, resulting in a triflate complex (*rac*)-**231** as an air stable red/orange powder (98%, Scheme 87).




(*rac*)-**207** (*rac*)-**231**

**Scheme 87** *Formation of amine tris(phenolate) titanium triflate complex (rac)-**231***

The $^1$H NMR of (*rac*)-**231** revealed that the resonances relating to both sets of the phenolate methyl groups had shifted to $\delta$ = 2.14 and 2.18 ppm. Interestingly at 0 °C, the signals corresponding to the benzylic protons, which had moved to $\delta$ = 3.09 and 4.04 ppm had become very broad and as such their multiplicity could not be resolved. It was proposed that this was due to the complex being slightly less stable due to the weakly coordinating triflate ligand, indicating that at room temperature, the enantiomers of (*rac*)-**231** were partially equilibrating as witnessed by the broadening of the benzylic protons. Variable temperature spectroscopic studies revealed that a temperature of 50 °C was necessary for complete racemisation to occur with the two benzylic protons coalescing to exhibit a broad peak at $\delta$ = 3.80 ppm (Figure 79). Alternatively, the

enantiomers of (*rac*)-**231** were configurationally stable at -50 °C, as shown by the appearance of two well defined doublets at δ = 3.37 and 4.35 ppm.

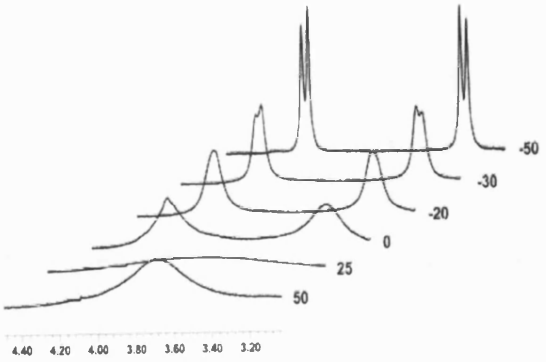



**Figure 79** *VT-NMR of (rac)-**231***

The structure of amine tris(phenolate) titanium triflate complex (*rac*)-**231** was determined by X-ray crystallography (Figure 80). This showed that the triflate bond to the titanium centre in complex (*rac*)-**231** was longer than the *iso*-propoxide bond in complex (*rac*)-**207** [Ti-O distances: 2.002(2)/2.017(2) Å for (*rac*)-**231** *vs.* 1.774(2)/1.776(2) Å for (*rac*)-**207**], implying that the triflate was more weakly coordinated to the metal centre. It was also evident that there was a concomitant shortening of the titanium-nitrogen bond in (*rac*)-**231** compared with (*rac*)-**207** [Ti-N distances: 2.216(2)/2.213(2) Å for (*rac*)-**231** *vs.* 2.303(2)/2.295(2) Å for (*rac*)-**207**, suggesting that the bonds are stronger. The titanium atom also sits slightly closer to the plane of the equatorial oxygen atoms [distance of Ti atom above the plane of the three phenolate O atoms: 0.188(1)/0.178(1) Å for (*rac*)-**231** *vs.* 0.251(1)/0.247(1) Å for (*rac*)-**207**]. This is probably due to the slight shortening of the bond between the titanium atom and the phenolate oxygen atom [average Ti-O(phenolate) distance: 1.797 Å for (*rac*)-**231** *vs.* 1.850 Å for (*rac*)-**207**]. The tilt of the propeller in both complexes is similar, with the angle in (*rac*)-**231** being slightly shallower [average angle between aryl planes and Ti-N bond vector: 13.0° for (*rac*)-**231** *vs.* 15.2° for (*rac*)-**207**].

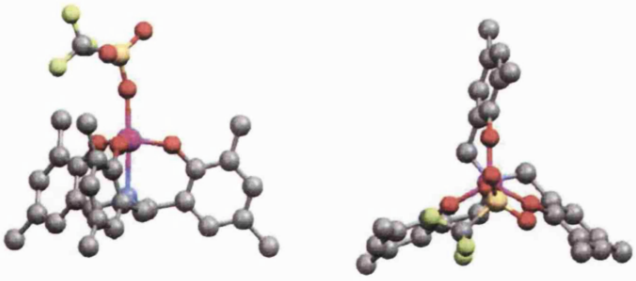
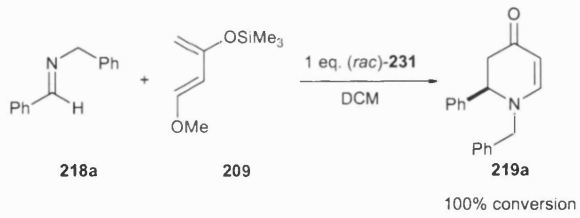


**Figure 80** *Side and top views (left and right respectively) of the X-ray crystal structure of complex (rac)-**231** (only one of two similar molecules found within the asymmetric unit shown and hydrogens omitted for clarity)*

## 2.5.5 Catalytic Screening of Triflate Complex (*rac*)-231

Amine tris(phenolate) titanium triflate complex (*rac*)-**231** was then screened for its catalytic activity in the *aza*-Diels Alder addition. It was decided to optimise its use as a Lewis acid catalyst for the formal *aza*-Diels Alder reaction between imine **218a** and Danishefsky's diene **209**, using the conditions discussed previously (section 2.5.3). Thus, one equivalent of catalyst (*rac*)-**231** was added to a solution of imine **218a** and 1.2 equivalents of Danishefsky's diene **209** in DCM (10 mL) (Scheme 88). Thin layer chromatography was performed immediately and it was discovered that the reaction had proceeded to completion within this time. This was obviously an exciting result as the equivalent reaction using titanium *iso*-propoxide catalyst (*R*)-**217** had required a reaction time of 5 hours (Scheme 75, Table 41, entry 1).[130]




**Scheme 88** *Aza-Diels Alder reaction catalysed by (rac)-**231***

## 2.5.6 Optimisation of Conditions

### Catalyst Loading

A series of reactions was then performed, to examine the performance of the catalyst in catalytic amounts, resulting in dihydropyridinone **219a** in moderate yields (18-36%) after column chromatography (Table 46). A reduction of the catalyst loading to 50 mol% resulted in *N*-benzyl-2,3-dihydro-2-phenyl-1H-pyridin-4-one **219a** in 34% isolated yield after 15 minutes (Table 46, entry 1). The presence of 10 mol% of (*rac*)-**231** resulted in dihydropyridinone **219a** in only 35% after 4 hours, although it was noted

that the reaction seemed to plateau after only 90 minutes (Table 46, entry 3). The reaction was also performed at -78 °C with 10 mol% of (*rac*)-**231**. After 2 hours dihydropyridinone **219a** was isolated in 35% yield (Table 46, entry 4). The use of 1 mol% of (*rac*)-**231** resulted in the product in a very disappointing 18% yield (Table 46, entry 5).

**Table 46**

| Entry | Catalyst mol% | Time | Isolated yield /% | Conversion[a] /% |
|---|---|---|---|---|
| 1 | 50 | 15 min | 34 | 99 |
| 2 | 20 | 70 min | 36 | 94 |
| 3 | 10 | 3 h | 35 | 96 |
| 4[b] | 10 | 2 h | 35 | 92 |
| 5 | 1 | 4 h | 18 | 61 |

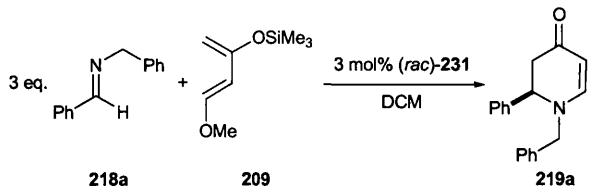
[a] Conversion measured *via* $^1$H NMR spectroscopic analysis; [b] Reaction performed at -78 °C

These results were pleasing as they confirmed that (*rac*)-**231** could catalyse the reaction at sub-stoichiometric amounts, although the yields were unacceptably low. Interestingly, examination of the $^1$H NMR spectra of the above reactions revealed that they had proceeded with excellent conversion of the imine (61-99%), though the isolated yield of the dihydropyridinone **219a** did not support this. As the dihydropyridinone products are stable under the aqueous work-up conditions and chromatography, it was proposed that the catalyst was so active that it was destroying either the imine before it reacted with the diene, or that the product was being destroyed. It was thus decided to repeat the reaction with an excess of the imine, in the hope that the yield would improve.

### Increasing the Equivalents of Imine and the Effect of Concentration

Using 3 mol% of (*rac*)-**231**, the reaction of 3 equivalents of imine **218a** with Danishefsky's diene **209**, afforded *N*-benzyl-2,3-dihydro-2-phenyl-1H-pyridin-4-one **219a** in an improved isolated yield of 69% after column chromatography (Scheme 89, Table 47, entry 1). However, the reaction time of 45 hours was unacceptably long. It was thus decided to examine the effect of concentration on the reaction process as all the previous reactions had been performed at relatively low concentration. As would be expected, decreasing the amount of solvent resulted in a corresponding decrease in reaction time, with a beneficial effect on the isolated yield. For example, performing the reaction in only 1 mL of DCM afforded the product after only 4 hours in 72% yield

(Table 47, entry 3). Interestingly, it was found that the reaction time also had an effect on the yield: for example, leaving the reaction in 1 mL of solvent for 24 hours instead of 4 hours, resulted in the product in a lower 52% yield (Table 47, entry 4), thus indicating degradation of the product under the reaction conditions and so close monitoring of the reaction was crucial. All consequent reactions were performed at the higher concentration of 0.42 M in DCM.




218a 209 219a

**Scheme 89** *Aza-Diels Alder reaction catalysed by (rac)-**231***

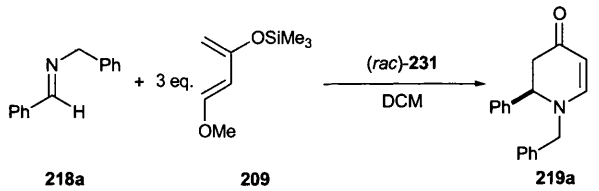
**Table 47**

| Entry | Concentration /M | Time /h | Isolated yield /% | Conversion[a] /% |
|---|---|---|---|---|
| 1 | 0.03 | 45 | 69 | 80 |
| 2 | 0.07 | 23 | 46 | 100 |
| 3 | 0.42 | 4 | 72 | 100 |
| 4 | 0.42 | 24 | 52 | 100 |

[a] Conversion measured *via* $^1$H NMR spectroscopic analysis

### Increasing the Equivalents of Danishefsky's Diene

As the increase of the amount of imine had improved the yield of the reaction, it was also decided to attempt the reaction with three equivalents of Danishefsky's diene and compare the results (Scheme 90, Table 48). It was hoped that increasing the equivalents of diene would also improve yield and conversion of the reaction. For example, the reaction between imine **218a** and three equivalents of Danishefsky's diene **209** in the presence of 3 mol% of (*rac*)-**231** resulted in dihydropyridinone **219a** in 72% yield and 65% conversion (Table 48, entry 1). The reaction in the presence of 10 mol% proceeded to completion after 45 minutes, affording **219a** in 69% yield (Table 48, entry 2). The use of 30 mol% of (*rac*)-**231** resulted in the product in 71% yield after only 15 minutes; this yield decreased to 62% when the reaction was left for 100 minutes (Table 48, entry 3).




218a 209 219a

**Scheme 90** *Aza-Diels Alder reaction catalysed by (rac)-**231***

**Table 48**

| Entry | Catalyst mol% | Time /min | Isolated yield /% | Conversion[a] /% |
|---|---|---|---|---|
| 1 | 3 | 45 | 72 | 65 |
| 2 | 10 | 45 | 69 | 100 |
| 3 | 30 | 15 | 71 | 100 |
| 4 | 30 | 100 | 62 | 100 |

[a] Conversion measured *via* $^1$H NMR spectroscopic analysis

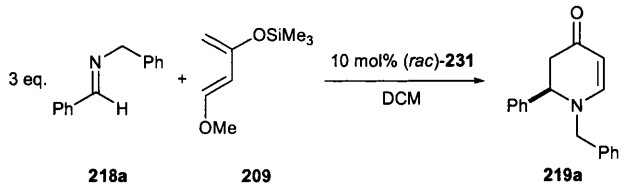
From a practical perspective, it was worthy of note that when an excess of Danishefsky's diene was used in the reaction, the yield was dependent on the reaction time, yet when three equivalents of imine was used, this effect was not observed.

### Work-up and Purification

It was a concern that the aqueous work up may be affecting the observed results of the reaction and as it was felt unnecessary as the catalyst did not seem to be hydrolysed or removed from the reaction mixture through this procedure. It was therefore decided to attempt the reaction without an aqueous work up. It was decided to compare the results of using three equivalents of imine with those of using three equivalents of diene, to determine whether either set of conditions proved superior. The reactions were performed with a catalyst loading of 10 mol% as this amount of catalyst consistently resulted in 100% conversion.

#### Three Equivalents of Imine

A reaction was performed with the higher catalyst loading of 10 mol% and after 2 hours the reaction mixture was evaporated and the crude residue pre-absorbed onto silica (0.5 g), before column chromatography. This resulted in the product in 60% isolated yield at 90% conversion (Table 49, entry 1). Leaving the reaction for 15 hours did not greatly improve the yield or the conversion (64% and 95% respectively) (Table 49, entry 2).




**Scheme 91** *Aza-Diels Alder reaction catalysed by 10 mol% (rac)-**231***

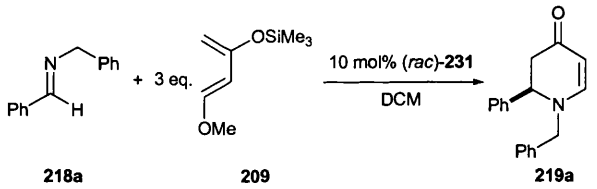
**Table 49**

| Entry | Catalyst mol% | Time /h | Isolated yield /% | Conversion[a] /% |
|---|---|---|---|---|
| 1 | 10 | 2 | 60 | 90 |
| 2 | 10 | 15 | 64 | 95 |

[a] Conversion measured *via* $^1$H NMR spectroscopic analysis

### Three Equivalents of Diene

The use of 10 mol% of complex (*rac*)-**231** in only 1 mL of DCM, resulted in 100% conversion of imine **218a** and three equivalents of diene **209** to *N*-benzyl-2,3-dihydro-2-phenyl-1H-pyridin-4-one **219a** (73% isolated yield) at room temperature in 45 minutes (Scheme 92, Table 50, entry 1). Different catalyst loadings were also examined under these conditions: 3 mol% of (*rac*)-**231** afforded dihydropyridinone **219a** in 65% yield (Table 50, entry 2), whilst 30 mol% resulted in **219a** in 59% yield (Table 50, entry 3). Thus, 10 mol% appeared to be the optimum amount of catalyst.




**Scheme 92** *Aza-Diels Alder reaction catalysed by (rac)-**231***

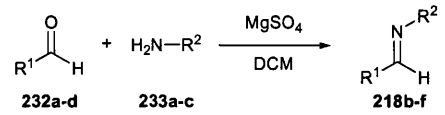
**Table 50**

| Entry | Catalyst mol% | Time /min | Isolated yield /% | Conversion[a] /% |
|---|---|---|---|---|
| 1 | 10 | 45 | 73 | 100 |
| 2 | 3 | 45 | 65 | 65 |
| 3 | 30 | 20 | 59 | 100 |

[a] Conversion measured *via* $^1$H NMR spectroscopic analysis

### 2.5.7 Application of the *Aza*-Diels Alder Reaction Catalysed by Complex (*rac*)-231 to a Range of Imines

The success of the reaction at high concentration with 10 mol% of (*rac*)-**231**, three equivalents of diene, and without an aqueous work up, proved optimal, and so these conditions were then applied to a representative range of *N*-benzyl-imines **218b-f**. They were first synthesised in the same way as imine **218a**, by treatment of the relevant aldehyde and amine with magnesium sulphate in DCM, using a modified literature procedure.[130] This resulted in the imines **218b-f** in good yields (Scheme 93, Table 51), the structures of which were confirmed by comparison of their $^1$H NMR spectra to known literature data.[130]

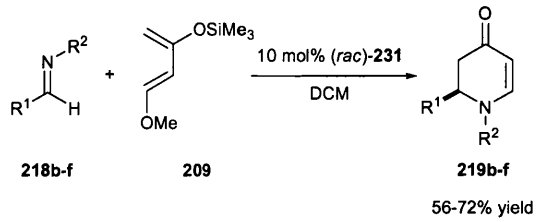



**Scheme 93** *Formation of imines **218b-f***

**Table 51**

| Product | $R^1$ | $R^2$ | Time /h | Yield /% |
|---|---|---|---|---|
| **218b** | 2-naphthyl | Bn | 3 | 95 |
| **218c** | 3,5-$(MeO)_2(C_6H_3)$ | Bn | 6 | 89 |
| **218d** | $^c$hexyl | Bn | 3 | 88 |
| **218e** | Ph | $^i$Pr | 4 | 92 |
| **218f** | Ph | 3,4-$(MeO)_2(C_6H_3)$ | 4 | 96 |

Subsequent reaction of these imines with Danishefsky's diene in the presence of 10 mol% of (*rac*)-**231** resulted in the corresponding 2,3-dihydro-pyridin-4-ones **219b-f** in good yields and with reaction times of less than 80 minutes in all cases (Table 52). $^1$H NMR spectroscopic analysis of the crude reaction products revealed that 2,3-dihydro-pyridin-4-ones **219b-f** were formed in 100% conversion as the only products in this reaction. Their structures were confirmed by comparison of their spectroscopic data to the literature.[130]




**Scheme 94** *Aza-Diels Alder reaction between imines **218b-f** and Danishefsky's diene **209**, catalysed by (rac)-**231***

**Table 52**

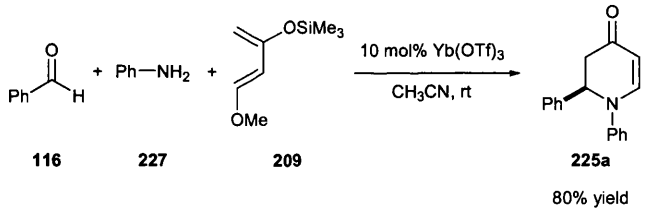
| Product | $R^1$ | $R^2$ | Time /min | Yield[a] /% |
|---|---|---|---|---|
| **219b** | 2-naphthyl | Bn | 40 | 71 |
| **219c** | 3,5-$(MeO)_2$Ph | Bn | 70 | 60 |
| **219d** | $^c$hexyl | Bn | 45 | 56 |
| **219e** | Ph | $^i$Pr | 60 | 72 |
| **219f** | Ph | 3,4-$(MeO)_2$Bn | 80 | 62 |

[a] All yields for chromatographically pure compounds.

These results compare favourably with previously reported systems, in particular those reported by Yamamoto *et al.*,[130] Creswell *et al.*,[135] and Frost and Weller *et al.*[136] (see section 2.5.3).

## 2.6 One-pot, Three-Component Coupling

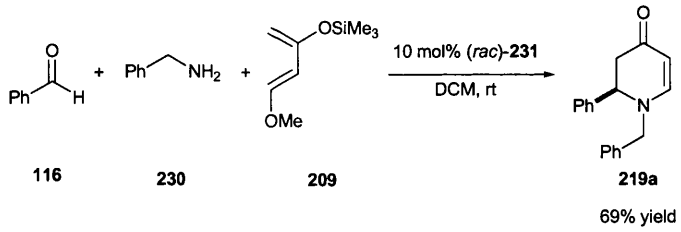
Due to the good results obtained in the *aza*-Diels Alder reaction catalysed by (*rac*)-**231**, it was decided to attempt a one-pot, three-component coupling reaction. This involves the *in situ* formation of an imine from its constituent amine and aldehyde in the presence of a Lewis acid, followed by addition of a diene, to yield the corresponding dihydropyridinone. This approach was previously published by Kobayashi *et al.* using ytterbium(III) triflate as the Lewis acid catalyst to yield dihydropyridinone **225a** in 80% yield (Section 2.5.3, Scheme 95).[134]




**Scheme 95** *One-pot, three-component coupling reaction catalysed by Yb(OTf)$_3$*

### 2.6.1 One-pot, Three-Component Coupling Catalysed by (*rac*)-231

Benzaldehyde **116** and benzylamine **230** were stirred together in DCM in the presence of (*rac*)-**231** and 4Å molecular sieves for one hour. After this time three equivalents of Danishefsky's diene **209** were added and the reaction mixture was stirred for a further 5 hours before the solvent was removed and the crude residue was pre-absorbed onto silica. Column chromatography yielded the product in 69% (Scheme 96).




**Scheme 96** *A one-pot, three-component coupling reaction catalysed by (rac)-**231***

## 2.7 Chiral *Aza*-Diels Alder Reaction

The success of the *aza*-Diels Alder reactions between imines **218a-g** and Danishefsky's diene **209**, has proven (*rac*)-**231** to be an efficient catalyst for this reaction. It was decided to attempt an *aza*-Diels Alder with a chiral imine to determine whether any diastereoselectivity could be induced, because despite (*rac*)-**231** being racemic there was NMR evidence of interconversion between the two enantiomers. This meant that there was a potential for a chiral auxiliary to lock the propeller chirality of the coordinated complex to form a single diastereomer. This strategy has been shown to be effective in the aluminium tris(2,6-diphenylphenoxide) (ATPH) **234** catalysed asymmetric Michael addition of a range of organolithiums to chiral ester **235** resulting in products **236a-f** in 90-99% yield and 91-99% de (Figure 81, Scheme 97, Table 53).[138]

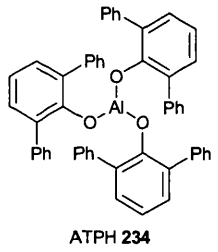
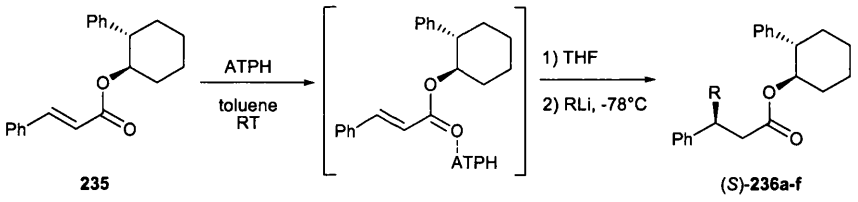
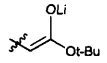
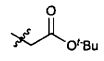



**Figure 81** *Aluminium tris(2,6-diphenylphenoxide) (ATPH) **234***




**Scheme 97** *Asymmetric Michael addition catalysed by ATPH **234***

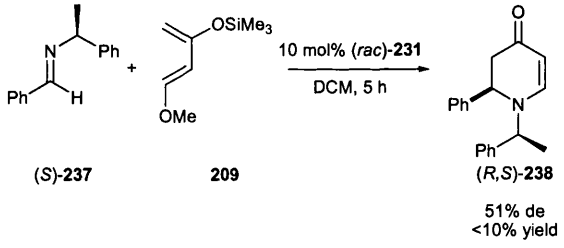
**Table 53**

| Nucleophile | Product | R | Yield /% | de /% |
|---|---|---|---|---|
| BuLi | **236a** | Bu | 99 | 97 |
| prenyl-Li | **236b** |  | 98 | α: 91 |
| | **236c** |  | | γ: 99 |
| 2-propenyl-Li | **236d** |  | 99 | 99 |
| vinyl-Li | **236e** |  | 94 | 98 |
|  | **236f** |  | 90 | 93 |

Despite ATPH having rapidly inter-converting conformational enantiomers, it was found that on binding to the optically pure ester these enantiomers were resolved to afford a diastereomerically pure complex. It was also evident that the diastereoselectivity was induced by the conformational chirality of the ATPH that is in turn dictated by the chirality of the ester.

### 2.7.1 Chiral *Aza*-Diels Alder Reaction Catalysed by (*rac*)-231

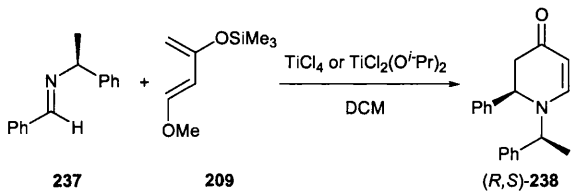
Thus, in order to probe the reaction mechanism of the *aza*-Diels Alder reaction catalysed by titanium complex (*rac*)-**231**, it was decided to attempt the *aza*-Diels Alder of a chiral imine derived from α-methyl benzylamine (Scheme 98), to determine whether any diastereoselectivity would be induced.




**Scheme 98** *Aza-Diels Alder between (S)-N-benzylidene-1-phenylethanamine* ***237*** *and Danishefsky's diene* ***209*** *catalysed by 10 mol% (rac)-****231***

(*S*)-*N*-Benzylidene-1-phenylethanamine **237** was synthesised in 95% yield in the same manner as the other imines, and its structure was confirmed by comparison of the spectroscopic data with literature values.[130] The *aza*-Diels Alder reaction was performed under the standard conditions, resulting in (*R*)-2-phenyl-1-((*S*)-1-phenyl ethyl)-2,3-dihydropyridin-4(1H)-one **238** in less than 10% yield after column chromatography. Its structure was confirmed by comparison of the $^1$H NMR data to the

literature.[139] The low yield indicated that the increased steric bulk around the nitrogen of the imine interfered with the binding to the titanium complex. Analysis of the crude $^1$H NMR spectrum, by the integration of peaks corresponding to the major and minor diastereomers, revealed that the product was obtained in a diastereomeric excess of 51%. This result is lower than other examples of this reaction catalysed by titanium complexes in the literature.[130] In studies to determine the effectiveness of Lewis acids for this reaction performed by Yamamoto *et al.*, the use of titanium(IV) chloride resulted in the product in 74% de (Scheme 99, Table 54, entry 1); titanium dichloro-di-*iso*-propoxide, however, resulted in the product in 90% de (Table 54, entry 2).




237 209 (*R,S*)-238

**Scheme 99** *Aza-Diels Alder between (S)-N-benzylidene-1-phenylethanamine **237** and Danishefsky's diene **209** catalysed by $TiCl_4$ and $TiCl_2(O^iPr)_2$*

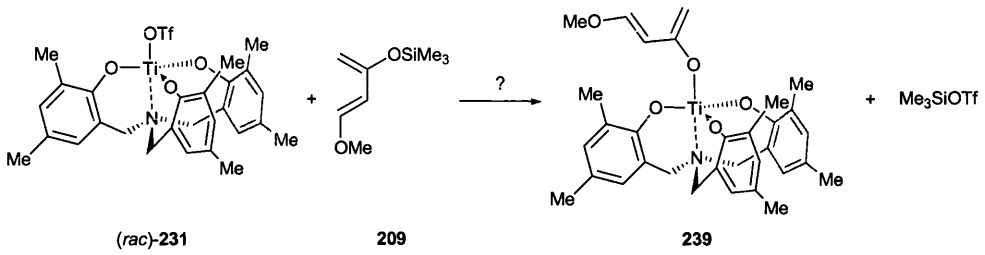
**Table 54**

| Entry | Lewis Acid | Equivalents | Yield /% | de /% |
|---|---|---|---|---|
| 1 | $TiCl_4$ | 1.0 | 7 | 74 |
| 2 | $TiCl_2(O^iPr)_2$ | 1.5 | 56 | 90 |

Thus, (*rac*)-**231** was shown to be less diastereoselective than both titanium dichloro-di-*iso*-propoxide, and titanium(IV) chloride. There are two possible explanations for this; one is that the two diastereomeric complexes which result from coordination of the imine are reacting under matched and mismatched control, with one diastereomer reacting in a more stereoselective manner than the other. The second possibility is that there is a dynamic kinetic resolution of the metal complex by the imine occurring, in a similar way to that observed with ATPH in the asymmetric Michael addition (Figure 81, Scheme 97). Thus, the complex is interconverting (albeit slowly) in the reaction mixture, with one enantiomer preferentially binding the imine. This shifts the equilibrium of the interconverting complexes in favour of this enantiomer, thus resulting in only one diastereomer of the bound complex, which then reacts with Danishefsky's diene in a mismatched fashion.

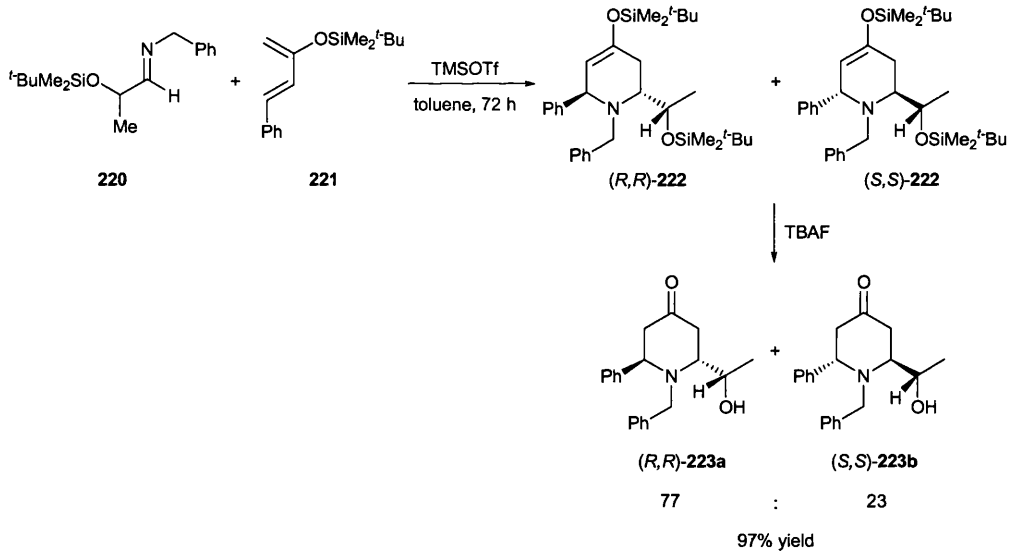
## 2.8 Is Complex (*rac*)-231 a Lewis Acid?

Although, Lewis acid activity had been demonstrated by complex (*rac*)-**231**, there was some concern that another mechanism was operating during the *aza*-Diels Alder reaction in order for the reaction to proceed. It was proposed that the trimethylsilyl group on the diene might have transmetallated with the triflate group on the titanium complex resulting in complex **239** (Scheme 100).



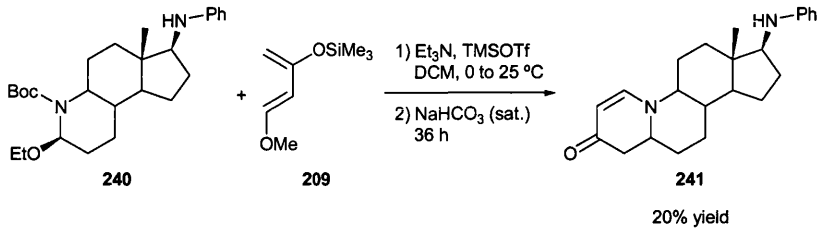

**Scheme 100** *Possible transmetallation during the reaction*

The side product of this reaction is trimethylsilyl triflate, which is also a Lewis acid known to be capable of catalysing the *aza*-Diels Alder Reaction.[132,140] For example, trimethylsilyl triflate has been shown previously to be an effective Lewis acid catalyst in the *aza*-Diels Alder reaction of α-silyloxy imine **220** with activated 2-silyloxy-1,3-diene **221** (Section 2.5.3, Scheme 77).[132] After treatment with TBAF, (2*R*,6*R*)-1-benzyl-2-((*S*)-1-hydroxyethyl)-6-phenylpiperidin-4-one **223a** was obtained in a diastereomeric ratio of 77:23 and an overall yield of 97% (Scheme 101).




**Scheme 101** *Aza-Diels Alder between α-silyloxy imine* ***220*** *and activated 2-silyloxy-1,3-diene* ***221***

Guarna *et al.* have reported the use of trimethylsilyl triflate to catalyse a formal *aza*-Diels Alder reaction in the synthesis of 17β-*N*-substituted 19-nor-10-azasteroids, such as **241**, as inhibitors of human 5α-reductases I and II.[140] The *in situ* formation of an imine from **240** followed by reaction with Danishefsky's diene catalysed by trimethylsilyl triflate, resulted in the formation of norazasteroid **241** in 20% yield after chromatography (Scheme 102).

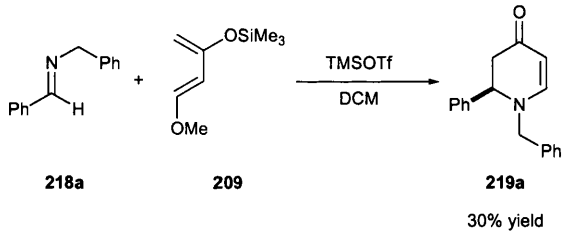



**Scheme 102** *Reaction of **240** and Danishefsky's diene **209** catalysed by TMSOTf*

## 2.8.1 Control Experiments

### *Aza*-Diels Alder Reaction Catalysed by Trimethylsilyl Triflate

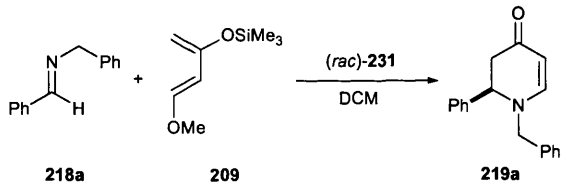
A series of control reactions were therefore undertaken to determine whether this transmetallation process might be occurring. The first step was to compare the results of the reaction catalysed with trimethylsilyl triflate with that catalysed by (*rac*)-**231**. To do this, the *aza*-Diels Alder between benzyl-phenylmethylene-amine **218a** and three equivalents of Danishefsky's diene **209** was performed in the presence of 10 mol% of trimethylsilyl triflate under the optimised conditions (Scheme 103). The reaction was deemed complete after one hour, after which the reaction was quenched with ammonium chloride and the solvent removed. Thin layer chromatography of the reaction mixture revealed a complex mixture of products and side products which was confirmed by analysis of the $^1$H NMR spectrum. Column chromatography led to the isolation of 1-benzyl-2-phenyl-2,3-dihydropyridin-4(1H)-one **219a** in a low 30% yield. This result therefore indicated that whilst it was feasible that trimethylsilyl triflate could be liberated under the reaction conditions, it was clear that high concentrations of trimethylsilyl triflate was not compatible with the formation of dihydropyridinone **219a** in high yield, as observed using $C_3$-complex (*rac*)-**231**.




**Scheme 103** *Aza-Diels Alder between benzyl-phenylmethylene-amine **218a** and Danishefsky's diene **209** catalysed by TMSOTf*

### Stoichiometric *Aza*-Diels Alder Reaction catalysed by (*rac*)-231

The reaction catalysed by 10 mol% (*rac*)-**231** was then repeated using equimolar amounts of Danishefsky's diene **209** and benzyl-phenylmethylene-amine **218a** (Scheme 104, Table 55, entry 1). After a reaction time of six hours (compared with 45 minutes for three equivalents of diene), analysis of the $^1$H NMR revealed that the reaction had proceeded to 90% conversion. This indicated that if the transmetallation mechanism was operating and the imine was being activated by trimethylsilyl triflate, then it was reacting with the remaining residual diene rather than the titanium enolate which had resulted from transmetallation of (*rac*)-**231** with the diene (Scheme 105). This result was confirmed by repeating the reaction using a catalyst loading of 50 mol%, which only proceeded to a 50% conversion after one hour (Table 55, entry 2).

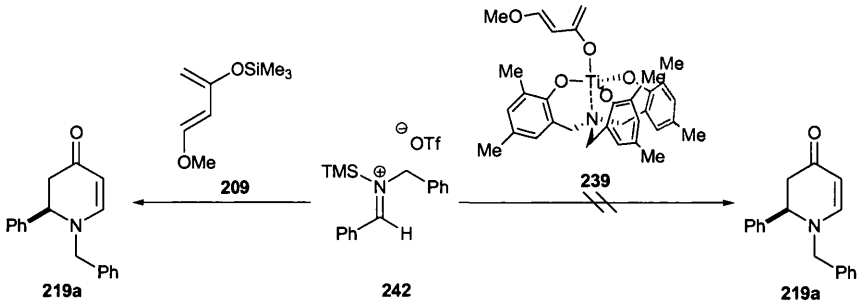



**Scheme 104** *Diels Alder reaction catalysed by (rac)-**231***

**Table 55**

| Entry | Catalyst mol% | Time /h | Conversion /% |
|---|---|---|---|
| 1 | 10 | 6 | 90 |
| 2 | 50 | 1 | 50 |

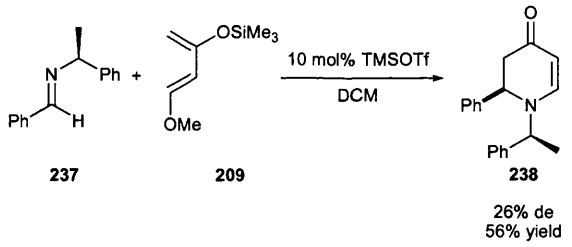
Clearly, the possible presence of a competing transmetallation mechanism to afford an imine complex **242** that could react with diene **209** to afford racemic **219a** had potentially fatal consequences for the development of an asymmetric variant of this type of *aza*-Diels Alder reaction using chiral analogues of triflate (*rac*)-**231**.




**Scheme 105** *Possible reaction of proposed imine complex* ***242***

### Chiral *Aza*-Diels Alder Reaction Catalysed by Trimethylsilyl Triflate

Consequently, it was decided to repeat the reaction using chiral imine **233** and Danishefsky's diene **209**, using trimethylsilyl triflate since an examination of the observed levels of stereocontrol might provide us with some clues as to which catalytic species was operating in the (*rac*)-**231** mediated *aza*-Diels Alder reaction. The *aza*-Diels Alder reaction using 10 mol% trimethylsilyl triflate was carried out under identical conditions to those used previously (Scheme 106). The dihydropyridinone product **238** was obtained in 26% de (c.f. 51% de with (*rac*)-**231**), thus confirming that complex (*rac*)-**231** is certainly involved as a catalyst in the reaction, whether as a titanium enolate of the diene component, or complexed to the imine. However, a competing transmetallation pathway resulting in formation of trimethylsilyl triflate may also be involved in (*rac*)-**231** mediated catalysis of this reaction, and is possibly responsible for the poorer de observed for the formation of **238** when using (*rac*)-**231** than was observed using titanium(IV) chloride (see Scheme 99).




**Scheme 106** *Aza-Diels Alder between (S)-N-benzylidene-1-phenylethanamine* ***237*** *and Danishefsky's diene* ***209*** *catalysed by 10 mol% trimethylsilyl triflate*

## 2.8.2 NMR Studies

Thus, two NMR experiments were performed to try to identify whether the proposed transmetallation mechanism was viable (Appendix 1). Firstly, a $^{1}H$ NMR was performed on a stoichiometric mixture of imine **218a** and (*rac*)-**231**, which revealed small changes in the signals relating to (*rac*)-**231** (Figure 82, Figure 83, Figure 84). For

example, the two singlets corresponding to the aryl methyl groups were seen to be separated by 0.1 ppm (c.f. 0.04 ppm for (*rac*)-**231**). More significantly, the two broad singlets representing the benzylic protons of the ligand had become more resolved and the gap between them had widened to 1.21 ppm (0.9 ppm for (*rac*)-**231**). The chemical shifts relating to the aryl groups of the imine were also shown to significantly change and had become much more diverse, though the peaks corresponding to the benzylic protons and the imine proton were relatively unchanged (Figure 83, Figure 84). A peak was also observed at $\delta$ = 9.92 ppm (not shown), which whilst it could correspond to benzaldehyde, indicating degradation of the imine, there was no evidence of the presence of the corresponding benzylamine. The differences in these spectra indicated that some interaction between the imine and complex (*rac*)-**231** was occurring.

The second NMR experiment performed was on a stoichiometric mixture of Danishefsky's diene **209** and titanium complex (*rac*)-**231** (Figure 85, Figure 86, Figure 87). Interestingly, there was no evidence of the diene **209** in the $^{1}$H NMR spectrum, with only the methyl ketone **243** being present (c.f. Figure 86). This was evidenced by the following chemical shifts: $\delta$ = 2.10 ppm corresponding to the methyl group of the ketone, which is shifted 0.09 ppm downfield from the expected chemical shift ($\delta$ = 2.01 ppm); $\delta$ = 3.78 ppm relating to the methoxy group (shifted downfield 0.28 ppm); a doublet at $\delta$ = 5.55 ppm corresponding to the alkene proton adjacent to the ketone (shifted downfield 0.15 ppm); $\delta$ = 7.42 ppm representing the alkene proton adjacent to the methoxy group (shifted downfield 0.03 ppm). The spectrum of complex (*rac*)-**231** was significantly altered with the two broad singlets representing the benzylic protons of the ligand being resolved into a sharp broad singlet at $\delta$ = 3.59 ppm. The two singlets corresponding to the aryl methyl groups of the ligand were seen to shift apart by 0.06 ppm (c.f. 0.04 ppm for (*rac*)-**231**). Another minor species also appeared to be represented by a resolved doublet at $\delta$ = 4.01 pm representing the benzylic protons, two singlets at $\delta$ = 2.20 and 2.28 ppm corresponding to the aryl methyl groups, and $\delta$ = 7.20 and 7.60 ppm corresponding to the aryl protons. These changes in the $^{1}$H NMR spectra seem to confirm that interaction between Danishefsky's diene **209** and titanium complex (*rac*)-**231** was occurring.

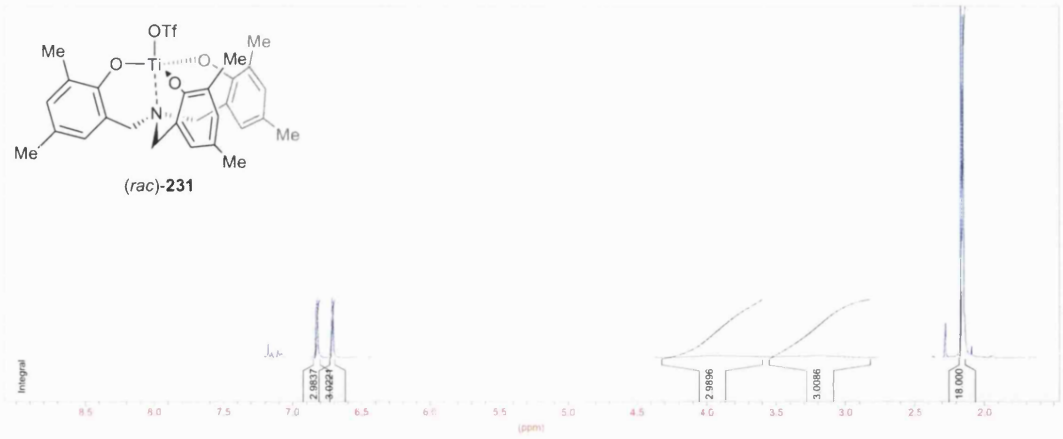



**Figure 82** *$^1$H NMR spectrum of complex (rac)-**231***

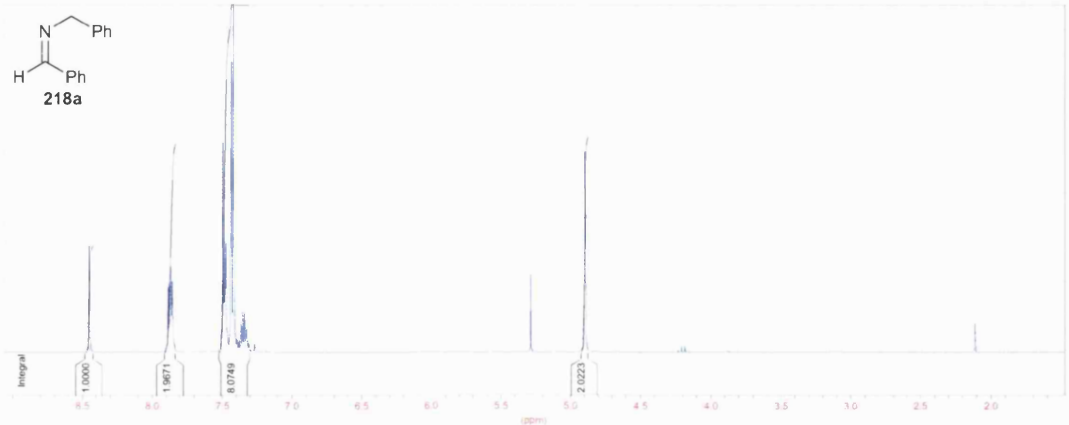



**Figure 83** *$^1$H NMR spectrum of imine **218a***

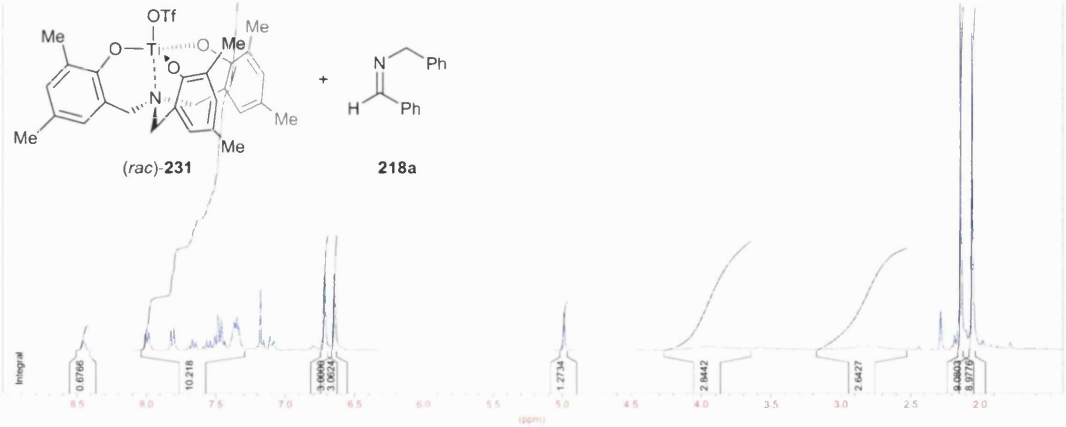



**Figure 84** *$^1$H NMR spectrum of the stoichiometric mixture of imine **218a** and (rac)-**231***

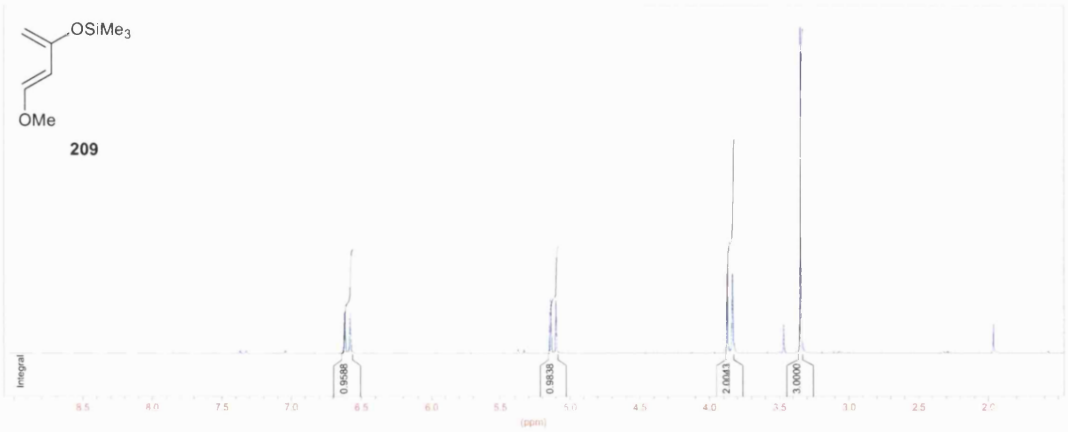



**Figure 85** *$^1$H NMR spectrum of Danishefsky's diene **209***

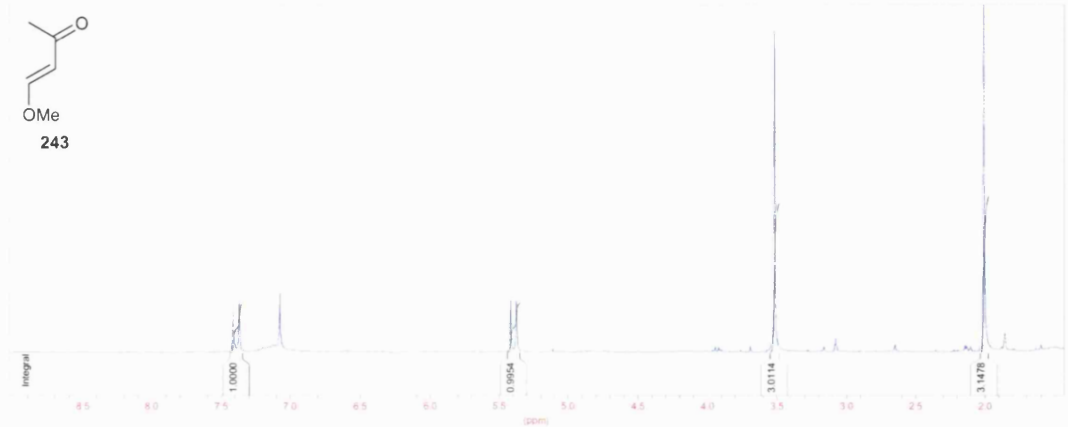



**Figure 86** *$^1$H NMR spectrum of methyl ketone **243***

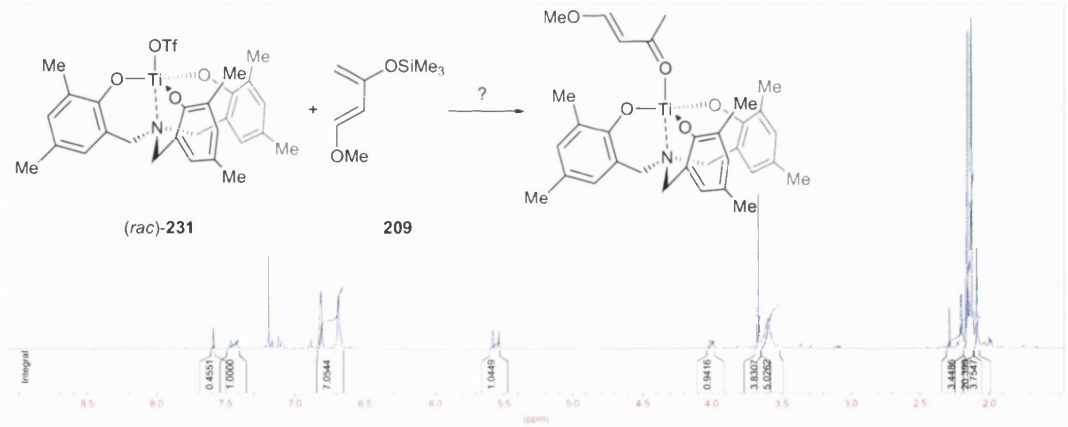



**Figure 87** *$^1$H NMR spectrum of the stoichiometric mixture of Danishefsky's diene **209** and (rac)-**231***

## 2.9 Conclusion

Thus, whilst it appeared that complex (*rac*)-**231** might not be wholly responsible for the catalysis of the *aza*-Diels Alder reactions described herein, it has been shown to be involved, due to the significant enhancement of the diastereoselectivity of the chiral Diels Alder reaction when compared to the reaction catalysed by trimethylsilyl triflate. Nevertheless, it was decided to screen further organic transformations in order to determine whether (*rac*)-**231** could be employed as a Lewis acid, particularly for transformations where competing transmetallation processes were unlikely to occur.

# CHAPTER 3:
# *Catalyst Screening*

# 3 CATALYST SCREENING

## 3.1 Aims and Objectives

The aim of this chapter was to screen complex (*rac*)-**231** as a catalyst in a range of organic transformations. Work focussed on transformations that would involve a titanium enolate or proceed *via* standard Lewis acid catalysis. This was an attempt to prove the synthetic potential of (*rac*)-**231** as a 'true' Lewis acid, as well as to identify transformations for screening using the equivalent chiral catalytic system. Complex (*rac*)-**231** could potentially be an ideal titanium triflate reagent for synthesis because it is air stable over a period of months with no significant loss of activity; thus, comparing favourably to traditional titanium triflate reagents, which are extremely moisture sensitive. However, this stability is likely to mean that it is less reactive and so it was necessary to screen (*rac*)-**231** in a wide range of transformations to determine its spectrum of catalytic activity.

## 3.2 Catalysis of a Range of Organic Transformations by (*rac*)-231

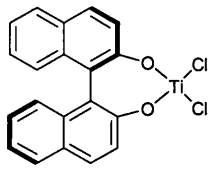
It was decided to screen (*rac*)-**231** in transformations that had been previously reported to be catalysed by titanium complexes, and in particular titanium-BINOL, alkoxide, or phenolate complexes. Reactions proceeding *via* titanium enolate intermediates were also considered. In 2003, a comprehensive review was published by Chen *et al.* detailing the applications of modified BINOL ligands for the formation of chiral metal complexes for asymmetric catalysis.[141] This prompted us to screen for activity of (*rac*)-**231** in the following reactions:

- Ene Reaction
- Allylation of benzaldehyde
- Diethyl zinc addition to benzaldehyde
- Conventional Diels Alder Reaction
- Michael Addition
- Aldol Reaction

Our first goal was to determine whether complex (*rac*)-**231** would be synthetically useful in transformations requiring a Lewis acid for catalysis. The first transformation screened for Lewis acid activity was the ene reaction.

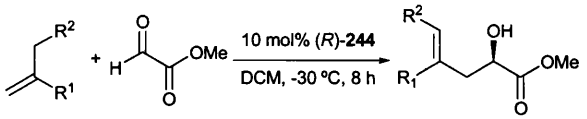
## 3.3 Ene Reaction

In 1990, the catalysis of an asymmetric glyoxylate-ene reaction by titanium(IV)-(*R*)-BINOL complex **244** was reported (Figure 88).[142] The reaction of methyl glyoxylate **245a** with a range of alkenes in the presence of 10 mol% (*R*)-**244** afforded (*R*)-α-hydroxy esters (*R*)-**247a-d** in good yields (72-97%) and moderate to good enantioselectivities (48-97%) (Scheme 107, Table 56). For example, the reaction with *iso*-butylene **245a**, resulted in (*R*)-methyl 2-hydroxy-4-methylpent-4-enoate **247a** in 95% ee and 72% yield after 8 hours (Table 56, entry 1). It was found that the reaction between methyl glyoxylate **246a** and α-methyl styrene **245b** only required 1 mol% of the catalyst affording α-hydroxy ester **247b** in 97% ee and 97% yield (Table 56, entry 3).




(*R*)-**244**

**Figure 88** *Titanium(IV)-(R)-BINOL complex* ***244***




**245a-d** **246a** (*R*)-**247a-d**

**Scheme 107** *Gyloxylate-ene Reaction with a range of alkenes catalysed by (R)-****244***

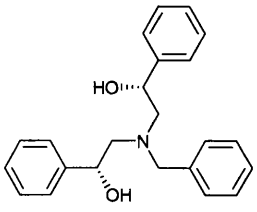
**Table 56**

| Entry | Product | $R^1$ | $R^2$ | Yield /% | ee /% |
|---|---|---|---|---|---|
| 1 | **247a** | Me | H | 72 | 95 |
| 2[a] | **247a** | Me | H | 79 | 7 |
| 3[b] | **247b** | Ph | H | 97 | 97 |
| 4 | **247c** | $-(CH_2)_4-$ | | 82 | 97 |
| 5 | **247d** | $-(CH_2)_3-$ | | 87 | 48 |

[a] In the absence of 4ÅMS; [b] 1 mol% of (*R*)-**244**

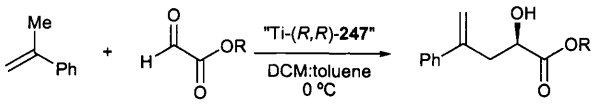
The presence of molecular sieves was found to be vital to the reactions; in their absence the reaction of methyl glyoxylate **246a** with *iso*-butylene **245a**, yielded α-hydroxy ester (*R*)-**247a** in only 7% ee ((Table 56, entry b). It was found that their inclusion during the formation of the catalyst was essential, as it was believed that they 'significantly facilitate' the alkoxy ligand exchange reaction of the catalyst.

The titanium complex of (*R*,*R*)-**248** was shown to promote asymmetric glyoxylate-ene reactions with α-methyl styrene and a range of glyoxylates **246a-d** at 0 °C (Scheme 108, Table 57).[143] The resulting α-hydroxy esters **249a-d** were obtained in moderate yields (43-56%), with only the product derived from methyl glyoxylate having its enantiomeric excess determined (48%).




(*R*,*R*)-**248**

**Figure 89** *$C_2$-symmetric tridentate ligand (R,R)-**248***




**245b** **246a-d** **249a-d**

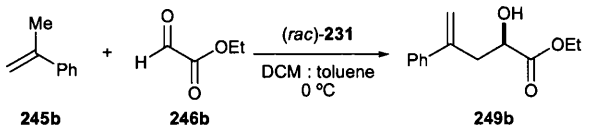
**Scheme 108** *Ene reaction catalysed by an in situ titanium complex of (R,R)-**248***

**Table 57**

| Product | R | Yield /% | ee /% |
|---|---|---|---|
| **249a** | Me | 56 | 48 |
| **249b** | Et | 52 | - |
| **249c** | $^{n}$Bu | 48 | - |
| **249d** | Bn | 43 | - |

### 3.3.1 Ene Reaction catalysed by (*rac*)-231

Due to the similarities between (*R*,*R*)-**248** which was reported by Sundarajan *et al.*[143] (Section 3.3, Figure 89) and ligand **200** of (*rac*)-**231** it was decided to attempt to emulate the activity of the titanium complex of (*R*,*R*)-**231** in the ene reaction. The reaction chosen was the ene reaction between ethyl glyoxylate **246b** and α-methyl styrene (Scheme 109). Despite numerous attempts, product **249b** was only observed in trace amounts after 24 hours and so investigation of this reaction was not pursued further.




**Scheme 109** *Ene reaction catalysed by (rac)-**231***

## 3.4 Allylation Reactions

In 2000, Doucet *et al.* reported a reproducible enantioselective titanium(IV)-(*R*)-BINOL catalysed addition of allyltributyltin to aldehydes **251a-e** (Figure 90, Scheme 110, Table 58).[144] Previously, the titanium catalysts used for allylation reactions required extremely dry conditions in DCM at low temperatures, and was consequently difficult to reproduce.[145] The active catalyst was found to be more stable in toluene than DCM and the reaction could be performed at room temperature without degradation of the enantioselectivity. For example, the allylation of 4-trifluoromethylbenzaldehyde **251a** in toluene resulted in alcohol **253a** in 90% ee and 100% yield compared with 87% ee and 95% yield for the analogous reaction in DCM (Table 58, entries 1 and 2). It was also found that the absence of molecular sieves actually improved the enantioselectivity of the reaction (97% versus 90% ee) (Table 58, entries 2 and 3).

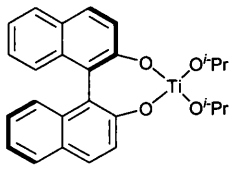
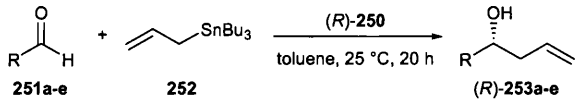



**Figure 90** *Titanium(IV)-(R)-BINOL complex (R)-**250***




**Scheme 110** *Allylation of a range of aldehydes catalysed by complex (R)-**250***

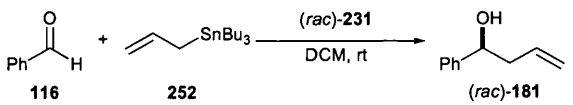
**Table 58**

| Entry | Product | R | Yield /% | ee /% |
|---|---|---|---|---|
| 1[a] | **253a** | 4-$CF_3(C_6H_4)$ | 95 | 87 |
| 2[b] | **253a** | 4-$CF_3(C_6H_4)$ | 100 | 90 |
| 3 | **253a** | 4-$CF_3(C_6H_4)$ | 94 | 97 |
| 4 | **253b** | 3-$CF_3(C_6H_4)$ | 96 | 97 |
| 5 | **253c** | 3,5-$CF_3(C_6H_4)$ | 92 | 91 |
| 6 | **253d** | 4-$F(C_6H_4)$ | 95 | 97 |
| 7 | **253e** | 4-$Cl(C_6H_4)$ | 3 | 96 |
| 8 | **253f** | 4-$Br(C_6H_4)$ | 58 | 97 |

[a] Reaction performed in DCM in the presence of 4ÅMS; [b] In the presence of 4ÅMS

### 3.4.1 Allylation of benzaldehyde catalysed by (*rac*)-231

The allylation of benzaldehyde with allyltributyltin was attempted following the procedure published by Doucet *et al.* in 2000 (Section 3.4).[144] Consequently benzaldehyde **116** and allyltributyltin **252** were treated with 50 mol% of (*rac*)-**231** (Scheme 111, Table 59, entry 1). The reaction was monitored by TLC and it was pleasing to find that the reaction was complete after only 30 minutes, affording (*rac*)-1-phenylbut-3-en-1-ol **181** in 75% yield. This was surprising as the reaction reported by Doucet *et al.*, using a titanium(IV)-(*R*)-BINOL complex required a reaction time of 20 hours.[144] The product was identified by analysis of its $^1$H NMR spectrum which was compared to the literature data.[146] Chemical shifts corresponding to the newly formed secondary alcohol were observed at $\delta$ = 4.65 ppm (methine proton) and $\delta$ = 2.10 ppm (alcoholic proton). Due to the success of the reaction catalysed by 50 mol%, it was repeated with a lower catalyst loading of only 5 mol%; this resulted in (*rac*)-1-phenylbut-3-en-1-ol **181** in 64% yield after 4 hours (Table 59, entry 2). These results were obviously very pleasing and application of this reaction to other classes of substrates is currently being investigated by another member of the SDB group.




116 252 (*rac*)-181

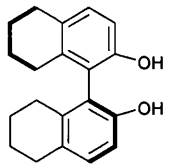
**Scheme 111** *Allylation of benzaldehyde with allyltributyltin catalysed by (rac)-**231***

**Table 59**

| Entry | Catalyst mol% | Time | Yield /% |
|---|---|---|---|
| 1 | 50 | 30 min | 75 |
| 2 | 5 | 4 h | 64 |

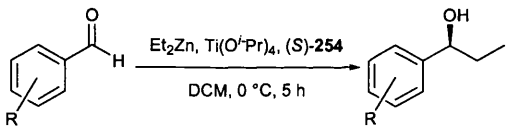
## 3.5 Organozinc Additions to Aldehydes

In 1997, Chan *et al.* reported the enantioselective addition of diethylzinc to aromatic aldehydes catalysed by titanium(IV) complexes of octahydro-BINOL derivative (*S*)-**254** (Figure 91).[147] It was found that an excess of titanium(IV) *iso*-propoxide was required for a high reaction rate and high enantioselectivity, with the optimal ratio of titanium(IV) *iso*-propoxide to (*S*)-**254** at 7:1. Under these conditions (*S*)-alcohols **256a-f** were obtained in 89-100% conversion and 94-98% ee, after 5 hours at 0°C (Scheme 112, Table 60). For example, addition of diethyl zinc to benzaldehyde resulted in (*S*)-1-phenylpropan-1-ol in 98% ee and 100% conversion (Table 60, entry 1). These results were found to be superior to those obtained using (*S*)-BINOL (73-94% ee), specifically the enantiomeric excess of (*S*)-1-phenylpropan-1-ol afforded from the reaction using (*S*)-BINOL was 92%.[148]




(*S*)-**254**

**Figure 91** *BINOL derivatives (S)-**254***




**255a-f** (*S*)-**256a-f**

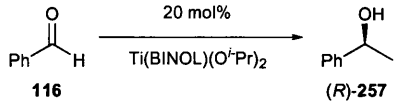
**Scheme 112** *Diethyl zinc addition to aldehydes catalysed by titanium(IV)-(S)-**254** complex*

**Table 60**

| Entry | Alcohol | R | Conversion /% | ee /% |
|---|---|---|---|---|
| 1 | **256a** | H | 100 | 98 |
| 2 | **256b** | 2-F | 100 | 94 |
| 3 | **256c** | 3-MeO | 100 | 96 |
| 4 | **256d** | 2-Cl | 99 | 96 |
| 5 | **256e** | 4-F | 100 | 97 |
| 6 | **256f** | 4-Cl | 89 | 97 |

It had been reported by Seebach *et al.* that dialkyl zinc is not directly responsible for the addition of the alkyl group to the aldehyde, but it actually transmetallates the alkyl group to the titanium complex.[149] To confirm this, Walsh *et al.* compared the reaction of dimethyl zinc and benzaldehyde with the reaction of benzaldehyde and methyl-

titanium(IV) *iso*-propoxide, both in the presence of a titanium(IV)-BINOL complex (Scheme 113, Table 61). These reactions resulted in (*R*)-1-phenylethan-1-ol **257** in identical enantioselectivities (50% ee and 49% ee respectively), proving that the dialkyl zinc is not involved in the reaction process and that the reaction must proceed *via* a titanium-alkyl intermediate.




**116** **(*R*)-257**

**Scheme 113** *Diethyl zinc addition to benzaldehyde* ***116***

**Table 61**

| Entry | Me Source | Equiv of Ti(O$^i$Pr)$_4$ | ee /% |
|---|---|---|---|
| 1 | $Me_2Zn$ | 1.2 | 50 |
| 2 | Me-Ti(O$^i$Pr)$_3$ | 0 | 49 |

The knowledge that the excess titanium(IV) *iso*-propoxide affects both the enantioselectivity and the rate of the reaction and that there must be a titanium-alkyl intermediate led to the proposal of a possible transition state for the addition of dialkyl zinc to aldehydes which involves a binuclear species (Figure 92).

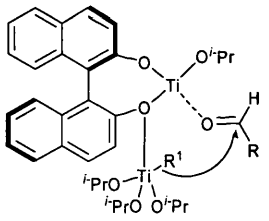
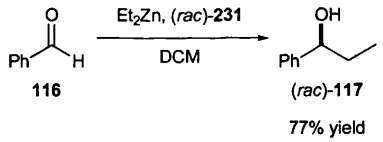



**Figure 92** *Possible intermediate for the addition of alkyl groups to aldehydes*

### 3.5.1 Diethyl zinc Addition to Benzaldehyde catalysed by (*rac*)-231

The addition of diethyl zinc to benzaldehyde is a common method to examine the activity of Lewis acid catalysts (Chapter 1).[141] To this end it was decided to attempt this reaction using 20 mol% of (*rac*)-**231** (Scheme 114). Treatment of a solution of (*rac*)-**231** with diethyl zinc at room temperature followed by benzaldehyde at 0 °C, resulted in the crude product as an orange oil after 6 hours. Subsequent column chromatography afforded (*rac*)-1-phenyl propanol **117** as a yellow oil in 77% yield. The product was identified by analysis of its $^1$H NMR spectrum and its comparison to literature data.[150]

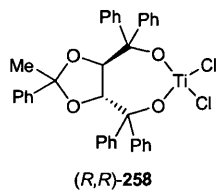



**Scheme 114** *Diethyl zinc addition to benzaldehyde* ***116*** *catalysed by (rac)-****231***

It is worthy of note that this reaction was complete in 6 hours with no additional titanium(IV) *iso*-propoxide added, as is usually required for the catalysis of this reaction by titanium complexes (Section 3.4). Once again, further applications of this reaction are being investigated by another member of the SDB group.

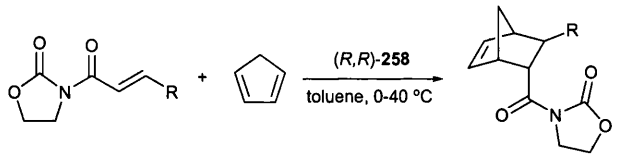
## 3.6 Conventional Diels Alder Reaction

Several accounts have been published regarding the use of TADDOL ligands in Diels Alder reactions since 1986 and 1987 when Narasaka *et al.*[151] and Seebach *et al.*[152] first reported their use for this transformation. In 1989, Narasaka *et al.* published a consolidation of their work regarding the asymmetric Diels Alder reaction between a range of *N*-acryloyloxazolidin-2-ones **155a-d** and cyclopentadiene **156** catalysed by chiral titanium complexes.[153] Several chiral diols were screened as ligands in these reactions and the best results were obtained with titanium complex **258** in which the alkyl groups on the acetal were not equivalent (Figure 93). It was also shown that sub-stoichiometric amounts of complex **258** could efficiently catalyse the Diels Alder reaction affording the bicyclic adducts in good yields (72-93%), *endo*:*exo* selectivities (88:12 to 96:4), and enantioselectivities (64-91%) (Scheme 115, Table 62). However, it was found necessary to perform the reactions in the presence of 4Å molecular sieves, as the enantioselectivities were very poor in their absence. Titanium-TADDOL complexes bound to polymers have also been shown to be efficient catalysts for these types of Diels Alder reactions.[154]




(*R,R*)-**258**

**Figure 93** *Ttitanium complex (R,R)-****258***




155a-d 156 (2S)-157a-d

**Scheme 115** *Diels Alder Reaction catalysed by (R,R)-**258***

**Table 62**

| Product | R | T /°C | Yield /% | *endo : exo* | *endo*-157 ee /% |
|---|---|---|---|---|---|
| **157a** | H | 40 | 93 | 96 : 4 | 64 |
| **157b** | Me | 0 | 87 | 92 : 8 | 91 |
| **157c** | Ph | rt | 72 | 88 : 12 | 64 |
| **157d** | $^{n}$Pr | 0 | 79 | 91 : 9 | 72 |

Subsequent papers have largely concentrated on the elucidation of the mechanism of this reaction and on the origin of the stereochemistry.[155] The first of this kind was published by Seebach *et al.*, which was a 'systematic investigation' into the Diels Alder reaction catalysed by titanium-TADDOL complexes, concentrating on the reaction of 3-butenoyl-1,3-oxazolidin-2-one with cyclopentadiene.[156] In this report, mechanistic models were proposed which enabled the prediction of the course of reactions mediated by titanium-TADDOL complexes. These models were found to also be applicable to the use of titanium-BINOL complexes. The model for the Diels Alder reaction of (*E*)-3-but-2-enoyloxazolidin-2-one **155b** catalysed by titanium complexes of (*S,S*)-TADDOLs or (*R*)-BINOL is depicted in Figure 94.

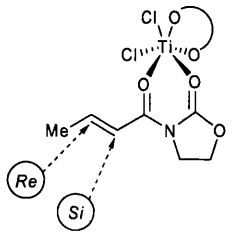
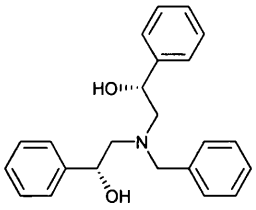



**Figure 94** *Mechanistic model proposed by Seebach et al. for the reaction of **155b** catalysed by (S,S)-TADDOLs*

In 1999, Sundarajan *et al.* reported the use of a titanium complex bearing $C_2$-symmetric tridentate ligand (*R,R*)-**248** (Figure 95), as a catalyst for asymmetric Diels Alder reactions (Scheme 116, Table 63).[143] This complex was generated *in situ* under three different reaction conditions and the mode of preparation was found to have an effect on the catalysis of the Diels Alder reaction. The most efficient method of preparation was

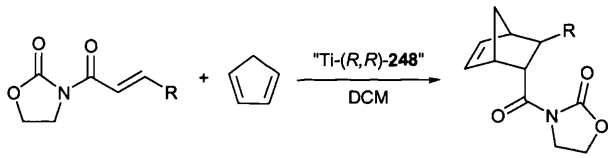
adding (*R*,*R*)-**248** to a 1:1 mixture of titanium(IV) *iso*-propoxide and titanium(IV) chloride. The removal of the solvents resulted in the titanium complex of (*R*,*R*)-**248** as a white powder, which was then used in the reactions. This complex was not characterised.




(*R*,*R*)-**248**

**Figure 95** *$C_2$-symmetric tridentate ligand (R,R)-**248***

Treatment of a range of *N*-acryloyloxazolidin-2-ones **155a-c** with cyclopentadiene **156** in the presence of one equivalent of the titanium complex of (*R*,*R*)-**248** resulted in the bicyclic 3-oxazolidin-2-ones **157a-c** with good *endo*:*exo* selectivity (84:16 to 90:10) and good yields (60-92%) (Scheme 116, Table 63). The enantioselectivities were moderate (20-53%), but were found to improve when the reaction temperature was lowered to -78 °C (Table 63, entries 3 and 5). The highest enantioselectivity was observed for the reaction between 3-((*E*)-3-phenylacryloyl)oxazolidin-2-one **155c** and cyclopentadiene **156** at -78 °C, resulting in 3-(5-phenylbicyclo[2.2.1]hept-2-ene carbonyl) oxazolidin-2-one **157c** in 75% ee, and *endo*:*exo* ratio of 85:15, and 51% yield (Table 63, entry 5).




**155a-c** **156** **157a-c**

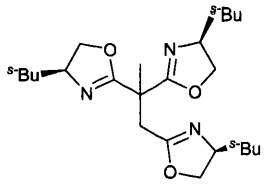
68-80% de
60-92% yield

**Scheme 116** *Diels Alder between N-acryloyloxazolidinones **155a-c** and cyclopentadiene **156** catalysed by the titanium complex of (R,R)-**248***

**Table 63**

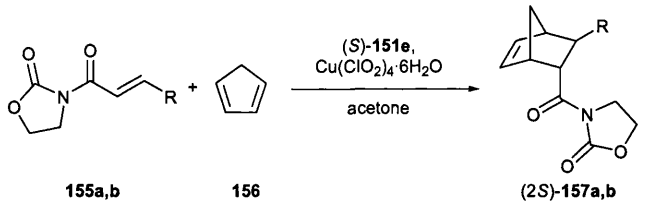
| Entry | Product | R | Time /h | T /°C | Yield /% | *endo : exo* | *endo*-157 ee /% |
|---|---|---|---|---|---|---|---|
| 1 | **157a** | H | 12 | rt | 85 | 84 : 16 | 53 |
| 2 | **157b** | Me | 8 | rt | 92 | 89 : 11 | 27 |
| 3 | **157b** | Me | 10 | -78 | 38 | 90 : 10 | 29 |
| 4 | **157c** | Ph | 6 | rt | 60 | 86 : 14 | 20 |
| 5 | **157c** | Ph | 10 | -78 | 51 | 85 : 15 | 75 |

There is also an example of a *pseudo*-$C_3$-symmetric ligand being applied to this Diels Alder reaction (Section 1.4.3). In 2004, Zhou *et al.* reported the use of ligand **151e** in copper catalysed Diels-Alder reactions between *N*-acryloyloxazolidin-2-one **155a** and cyclopentadiene **156** resulting in **157a** in a 75% ee and 99% yield with 93:7 *endo* selectivity at -20 °C (Scheme 117, Table 64, entry 1).[98] It was found that lowering the reaction temperature to -45 °C resulted in the (2*S*)-*endo*-product with a higher enantioselectivity (80% ee) and 99% yield (Table 64, entry 2). The reaction with **155b** was much slower, though it proceeded with high selectivity (81% ee) albeit with only 21% conversion after 48 hours (Table 64, entry 3). Increasing the temperature to 0 °C allowed 100% conversion, but the enantioselectivity dropped to 74% (Table 64, entry 4).




(*S*)-**151e**

**Figure 96** *Chiral trisoxazolines* ***151e***




**155a,b** **156** (2*S*)-**157a,b**

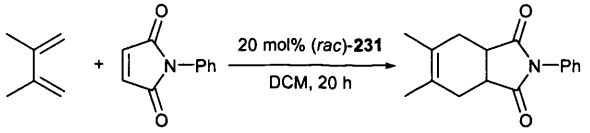
**Scheme 117** *Cu-catalysed Diels-Alder reactions between N-acryloyl-2-oxazolidinones* ***155a,b*** *and cyclopentadiene* ***156***

**Table 64**

| Entry | Product | R | T /°C | Time /h | Yield /% | *endo* : *exo* | *endo*-157 ee /% |
|---|---|---|---|---|---|---|---|
| 1 | **157a** | H | -20 | 3 | 99 | 93 : 7 | 75 |
| 2 | **157a** | H | -45 | 6 | 99 | 96 :4 | 80 |
| 3 | **157b** | Me | -20 | 48 | 21 | 90 : 10 | 81 |
| 4 | **157b** | Me | 0 | 48 | 99 | 81 : 19 | 74 |

### 3.6.1 Conventional Diels Alder catalysed by (*rac*)-231

It was decided to attempt the catalysis of a conventional Diels Alder reaction with complex (*rac*)-**231**. Treatment of 2,3-dimethyl-1,3-butadiene **259** and *N*-phenyl malimide **260** with 20 mol% of complex **231** resulted in 100% conversion after 20 hours, affording 3,4,7,8-tetrahydro-5,6-dimethyl-2-phenyl-2H-isoindole-1,3-dione **261**, in an isolated yield of 96% (Scheme 118). The structure of the product was confirmed by comparison of its spectroscopic data to that reported in the literature.[157]




**259** **260** **261**

96% yield

**Scheme 118** *Diels Alder reaction between 2,3-dimethyl-1,3-butadiene* ***259*** *and N-phenyl malimide* ***260*** *catalysed with 20 mol% (rac)-****231***

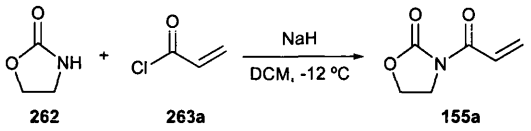
Whilst this result indicated some Lewis acidity, this Diels Alder reaction is normally considered to be facile, which was demonstrated by the fact that the reaction proceeded to 65% completion after 44 hours, without any catalyst being added!

### 3.6.2 Diels Alder between *N*-Acryloyloxazolidin-2-one 155a and Cyclopentadiene 156

The encouraging result of the reaction of *N*-phenylmalimide **260** and 2,3-dimethyl-1,3-butadiene **259** led to the decision to attempt the catalysis of the Diels Alder between *N*-acryloyloxazolidin-2-one **155a** and cyclopentadiene **156**. This dienophile was chosen because of its potential to coordinate in a bidentate fashion to the titanium complex. The catalysis of this type of Diels Alder reaction, by a chiral titanium complex that resembles (*rac*)-**231**, has previously been reported by Sundarajan *et al.* resulting in the bicyclic oxazolidin-2-ones in good yields (38-92%) and enantiomer excesses (20-75%) (Section 3.6).[143]

### Synthesis of *N*-Acryloyloxazolidin-2-one 155a

*N*-Acryloyloxazolidin-2-one **155a** was first synthesised *via* treatment of oxazolidin-2-one **262** with sodium hydride and acryloyl chloride **263a** in DCM overnight (Scheme 119). This resulted in *N*-acryloyloxazolidin-2-one **155a** as a crystalline solid after recrystallisation from ether and petroleum ether, in good yield (63%). Its structure was confirmed by comparison of its spectroscopic data to the literature.[158]

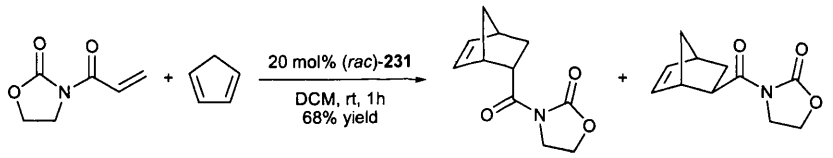



**262** **263a** **155a**

**Scheme 119** *Synthesis of N-Acryloyloxazolidin-2-one* ***155a***

### Diels Alder Catalysed by (*rac*)-231

Treatment of *N*-acryloyloxazolidin-2-one **155a** with cyclopentadiene **156** in the presence of 20 mol% (*rac*)-**231** after one hour resulted in 3-(bicyclo[2.2.1]hept-2-enecarbonyl) oxazolidin-2-one **157a**, in good yield (68%) after an aqueous work up and column chromatography (Scheme 120).




**155a** **156** **157a** *endo* major **157a** *exo*

**Scheme 120** *Diels Alder between N-acryloyloxazolidin-2-one* ***155a*** *and cyclopentadiene* ***156*** *catalysed by (rac)-****231***

Two diastereomers were observed in the $^1$H NMR spectrum and the major product was identified as the *endo* adduct by comparison of the $^1$H NMR data to the literature.[143] Characteristic signals of the bicyclic compound were observed as multiplets at $\delta$ = 1.30-1.46 and 1.84-1.94 ppm, corresponding to the two protons on C-7. Also observed were two doublets of doublets at $\delta$ = 5.81 and 6.18 ppm, which were assigned to the alkene protons (H-5 and H-6). The bridgehead protons (H-1 and H-4) were observed to have resonances at $\delta$ = 2.88 and 3.24 ppm as multiplets.

This result was very encouraging as (*rac*)-**231** now appears to be behaving unequivocally as a 'proper' Lewis acid catalyst.

### 3.6.3 Optimisation of Conditions

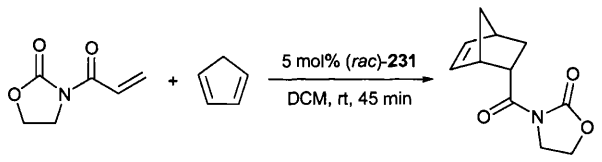
#### Work up and Purification

It was noted that, as in the case of the *aza*-Diels Alder, the aqueous work up did not remove/degrade the catalyst from the reaction mixture, the crude product was very clean, and no by-products were observed in the NMR spectra. The complex was also found to irreversibly bind to a silica column, regardless of the polarity of the solvent system used for elution and it was therefore decided that an aqueous work up was unnecessary and that filtering through silica would be sufficient to remove the catalyst.

Thus, repetition of the reaction of *N*-acryloyloxazolidin-2-one **155a** with cyclopentadiene **156** in the presence of 20 mol% (*rac*)-**231**, followed by filtration through silica, resulted in 3-(bicyclo[2.2.1]hept-2-enecarbonyl)oxazolidin-2-one **157a** in 66% yield. This reaction was monitored by HPLC (Daicel Chiralcel OD (94:6 Hex:IPA), flow = 1 mL $min^{-1}$), which revealed that the reaction was complete after only 15 minutes as determined by the absence of any starting material ($t_r$ = 34.18).

#### Catalyst Loading

Studies were then undertaken to optimise the catalyst loading for this reaction. As it had proceeded to completion in under 15 minutes in the presence of 20 mol% of (*rac*)-**231**, it was decided to attempt the reaction with only 5 mol% of (*rac*)-**231**. This reaction was also monitored by HPLC, which indicated that the reaction was complete after 45 minutes (Scheme 121).




**155a** **156** **157a**

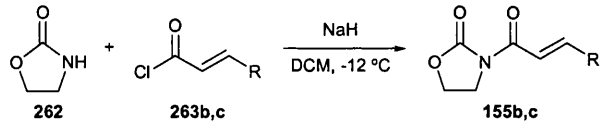
59% yield

**Scheme 121** *Diels Alder between N-Acryloyloxazolidin-2-one **155a** and Cyclopentadiene **156** catalysed by (rac)-**231***

The two main product peaks were observed in the chiral HPLC trace at $t_r$ = 26.9 and 30.1, which were assigned as the two *endo* enantiomers of the product, by comparison to the literature data.[159,160] The two *exo* peaks were observed to run together at $t_r$ = 25.4 min. The diastereomeric excess was measured to be 87% in favour of the *endo* form, which was confirmed by $^1$H NMR analysis.

### 3.6.4 Diels Alder Reaction using a Range of *N*-Acyloxazolidin-2-ones and Cyclopentadiene 156

Due to the success of the reaction between *N*-acryloyloxazolidin-2-one **155a** and cyclopentadiene **156**, it was decided to extend the study to a representative range of *N*-acryloyloxazolidin-2-ones, which were synthesised according to the procedure outlined for **155a**. Treatment of oxazolidin-2-one **262** with the corresponding acyl chloride resulted in the *N*-acryloyloxazolidin-2-ones **155b** and **155c** in good yields (83 and 53% respectively) (Scheme 122, Table 65), the structures of which were confirmed by comparison of $^1$H NMR data to the literature.[153]



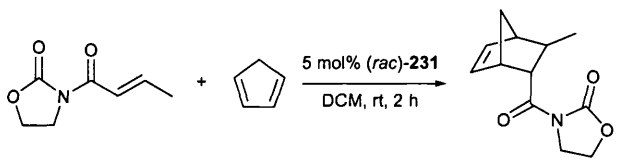

**Scheme 122** *Synthesis of N-Acyloxazolidin-2-ones **155b** and **155c***

**Table 65**

| Product | R | Yield /% |
|---|---|---|
| **155b** | Me | 83 |
| **155c** | Ph | 53 |

### 3.6.5 Diels Alder Reaction between (*E*)-*N*-But-2-enoyloxazolidin-2-one 155b and Cyclopentadiene 156

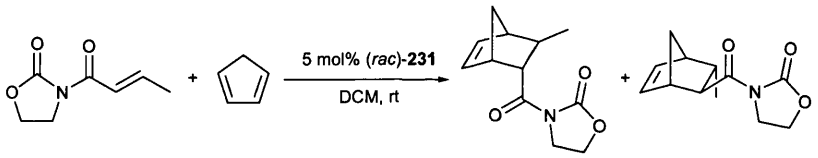
The first Diels Alder reaction attempted was that between (*E*)-*N*-but-2-enoyloxazolidin-2-one **155b** and cyclopentadiene **156** catalysed by 5 mol% of (*rac*)-**231**, followed by filtration through silica. After a reaction time of two hours the reaction was found to have proceeded to only 13% conversion (Scheme 123). Thus, it became evident that the reaction conditions would have to be optimised for each individual dienophile.




**Scheme 123** *Diels Alder reaction between (E)-3-but-2-enoyloxazolidin-2-one **155b** and cyclopentadiene catalysed by (rac)-**231***

### Catalyst Loading and Reaction Time

The catalyst loading was increased to 20 mol% and the reaction was monitored by chiral HPLC (Daicel Chiralcel AD, (19:1 Hex:IPA), flow = 1 mL $min^{-1}$).[159] After 4 hours, it was found to have proceeded to 70% conversion, with completion being observed after eight hours (Table 66). This was confirmed by $^1H$ NMR spectroscopy, which revealed that the starting material was no longer present. The major product was identified as the *endo* adduct which was confirmed by comparison of the $^1H$ NMR data to the literature and was obtained in an *endo*:*exo* ratio of 84:16.[143] The bicyclic nature of the product was evidenced by the peaks at $\delta$ = 1.40 and 1.63 ppm, which are characteristic of the two protons on the methylene bridge (C-7). The bridgehead protons were observed at $\delta$ = 2.47 and 3.21 ppm. Resonances at $\delta$ = 5.71 and 6.31 ppm corresponded to the alkene protons. The product was obtained after 8 hours in an isolated 78% yield and in 95% de after chromatographic purification.




**155b** **156** **157b** *endo* **157b** *exo*

**Scheme 124** *Diels Alder reaction between (E)-3-but-2-enoyloxazolidin-2-one and cyclopentadiene catalysed by (rac)-**231** monitored by HPLC*

**Table 66**

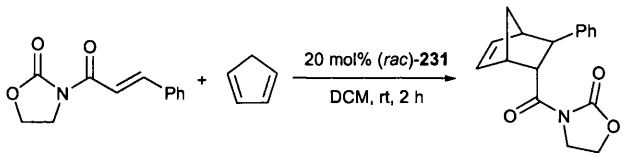
| Time /h | Conversion /% |
|---|---|
| 2 | 34 |
| 4 | 66 |
| 6 | 94 |
| 8 | 100 |

## 3.6.6 Diels Alder between *N*-[(*E*)-3-Phenylacryloyl]oxazolidin-2-one 155c and cyclopentadiene 156

The reaction between *N*-((*E*)-3-phenylacryloyl)oxazolidin-2-one **155c** and cyclopentadiene **156** was next examined. With the knowledge that this dienophile was likely to be less reactive then the previous dienophiles, it was decided to begin with the optimisation of the catalyst loading.

### Catalyst Loading and Temperature

The investigation was begun with 20 mol% of (*rac*)-**231**. The conversion of the reaction of *N*-((*E*)-3-phenylacryloyl)oxazolidin-2-one **155c** with cyclopentadiene was monitored with different reaction times and catalyst loadings (Scheme 125, Table 67). It was found that after 18 hours at room temperature in the presence of 20 mol% of complex (*rac*)-**231** the reaction had proceeded to only 34% conversion (Table 67, entry 1); after 48 hours the conversion had increased to 90% (Table 67, entry 2). It was then decided to increase the reaction temperature to investigate whether the reaction time would be shortened, however, even after 20 hours at 40 °C the conversion was only 58% (Table 67, entry 4). Increasing the temperature did not appear to have a great effect on the reaction rate, so it was decided to continue the investigations at room temperature.




155c 156 157c

**Scheme 125** *Diels Alder between 3-Cinnamoyloxazolidin-2-one **155c** and cyclopentadiene **156** catalysed by (rac)-**231***

**Table 67**

| Entry | Catalyst/ mol% | Time /h | T /°C | Conversion /% |
|---|---|---|---|---|
| 1 | 20 | 18 | rt | 34 |
| 2 | 20 | 48 | rt | 90 |
| 3 | 20 | 5 | 40 | 27 |
| 4 | 20 | 20 | 40 | 42 |
| 5 | 100 | 10 | rt | 66 |
| 6 | 100 | 18 | rt | 88 |

It was thus decided to increase the catalyst loading to 100 mol% in the hope of reducing the reaction time by a significant amount. The conversion was once again monitored over time, with disappointing results. The conversion rose to 66% after 10 hours (Table 67, entry 5), though disappointingly, the reaction had only proceeded to 88% conversion after 18 hours with 100 mol% of the catalyst (Table 67, entry 7).

### Effect of Concentration

As the reaction proved to be very slow at normal concentrations it was decided to perform the reaction at a higher concentration and compare the results. Treatment of *N*-cinnamoyloxazolidin-2-one **155c** with cyclopentadiene **156** in the presence of 100 mol% of (*rac*)-**231** at twice the concentration resulted in the product in 78% yield after 23 hours. Increasing the concentration to 0.5 mmol of dienophile in 2 mL of DCM, further reduced the reaction time to 6 hours with the product being obtained in 81% yield (Table 68, entry 2).

**Table 68**

| Entry | Concentration /M | Time /h | Conversion /% | Yield /% |
|---|---|---|---|---|
| 1 | 0.1 | 23 | 100 | 78 |
| 2 | 0.3 | 6 | 100 | 81 |

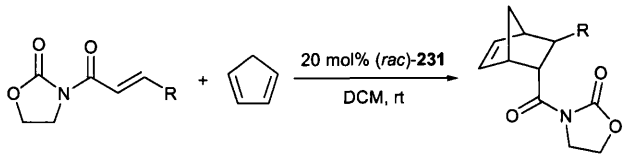
Two diastereomers were observed in the $^1$H NMR spectrum in an *endo:exo* ratio of 84:16. The major *endo* product was identified by the signals in the $^1$H NMR, which are characteristic of the bicyclic product. For example, resonance at $\delta$ = 1.18-1.98 ppm, corresponded to the protons on the methylene bridge (C-7). The bridgehead protons (H-1 and H-4) were observed at similar resonances as the proton on C-3, at $\delta$ = 2.93, 3.28, and 3.40 ppm. The resonances corresponding to the alkene protons were shown to be doublets of doublets at $\delta$ = 5.86 and 6.46 ppm. The diastereomeric excess of the purified *endo* adduct was obtained as >99% de *via* spectroscopic analysis of this region.

As the increase in concentration had a favourable effect on the reaction with no detrimental consequences it was decided to repeat all the reactions with the other dienophiles at this concentration, which would hopefully result in the products in optimised yields.

## 3.6.7 Diels Alder Catalysed by (*rac*)-231 under Optimised Conditions

Subsequent use of complex (*rac*)-**231** as a catalyst for the reaction of *N*-acryloyl-oxazolidinones **155a-c** with cyclopentadiene **156** afforded the corresponding *endo* bicyclic products **157a-c** in good yield (81-87%) and good *endo:exo* ratios (84:16 to >97:3) (Scheme 126, Table 69). The results for the reactions of all the *N*-acryloyl-oxazolidin-2-ones **155a-c** are shown in the table for comparison. The catalyst loading had to be altered for each dienophile; for example whilst *N*-acryloyloxazolidin-2-one **155a** only required 5 mol% of complex (*rac*)-**231** and the reaction was complete after only 30 minutes (Table 69, entry 1), *N*-((*E*)-3-phenyl-acryloyl)oxazolidin-2-one **155c**

required one equivalent of catalyst and a reaction time of 6 hours to achieve 100% conversion (Table 69, entry 3). The diastereomeric excesses were obtained *via* spectroscopic analysis.




**Scheme 126** *Diels Alder between N-acryloyl-oxazolidin-2-ones* ***155a-c*** *and cyclopentadiene* ***156*** *catalysed by (rac)-****231***

**Table 69**

| Entry | Product | R | Catalyst /mol% | Time /h | Yield /% | *endo*:*exo* |
|---|---|---|---|---|---|---|
| 1 | **155a** | H | 5 | 0.5 | 81 | >97 : 3 |
| 2 | **155b** | Me | 20 | 3 | 87 | 87 : 13 |
| 3 | **155c** | Ph | 100 | 6 | 81 | 84 : 16 |

### 3.6.8 NMR Studies

An NMR experiment was performed with a stoichiometric mixture of oxazolidin-2-one **155a** and (*rac*)-**231** (Appendix 1, Figure 82, Figure 98, Figure 99). This revealed a mixture of four possible species (**A-D**), including signals corresponding to a coordinated complex (**A**), and an uncoordinated complex (**B**). This is evidenced by the appearance of two new peaks relating to the aryl methyl groups of the coordinated complex (**A**) at $\delta$ = 2.09 and 2.20 ppm as well as two peaks corresponding to the uncoordinated species (**B**) at $\delta$ = 2.14 and 2.18 ppm (Figure 99). Four signals were also observed for the aromatic protons, $\delta$ = 6.68 and 6.89 ppm for the coordinated species and $\delta$ = 6.70 and 6.82 ppm for the uncoordinated complex. Another minor species (**C**) also appeared to be represented by two singlets at $\delta$ = 2.20 and 2.28 ppm corresponding to the aryl methyl groups, and $\delta$ = 7.20 and 7.60 ppm corresponding to the aryl protons. A chemical shift appeared to be overlapped with a resonance of oxazolidin-2-one **155a**, at $\delta$ = 4.01 pm, which is consistent with that observed for the experiment with Danishefsky's diene (Section 2.8.2). A further species (**D**) appears to be represented by two singlets at $\delta$ = 2.30 and 2.43 ppm corresponding to the aryl methyl groups, and $\delta$ = 6.91 and 7.00 ppm corresponding to the aryl protons. The presence of these species may be due to the degradation of the catalyst. The signals corresponding to **155a** appear

to be unmoved. The incomplete coordination of oxazoldin-2-one **155a** and (*rac*)-**231** maybe a contributing factor to the slightly lower activity of (*rac*)-**231** when compared to the *aza*-Diels Alder reaction.

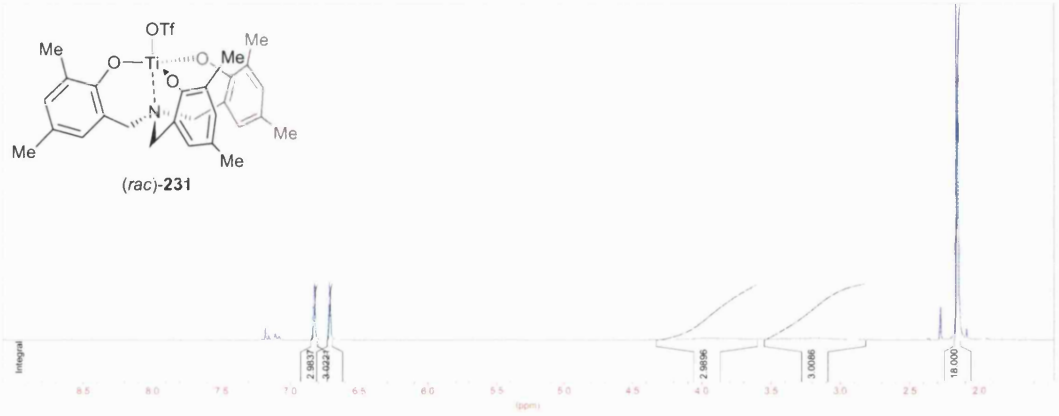



**Figure 97** *$^1$H NMR spectrum of complex (rac)-**231***

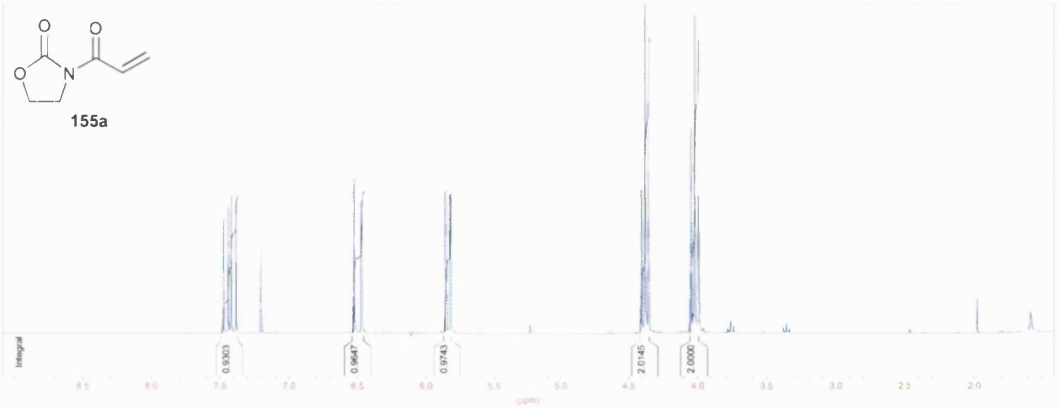



**Figure 98** *$^1$H NMR spectrum of oxazolidin-2-one **155a***

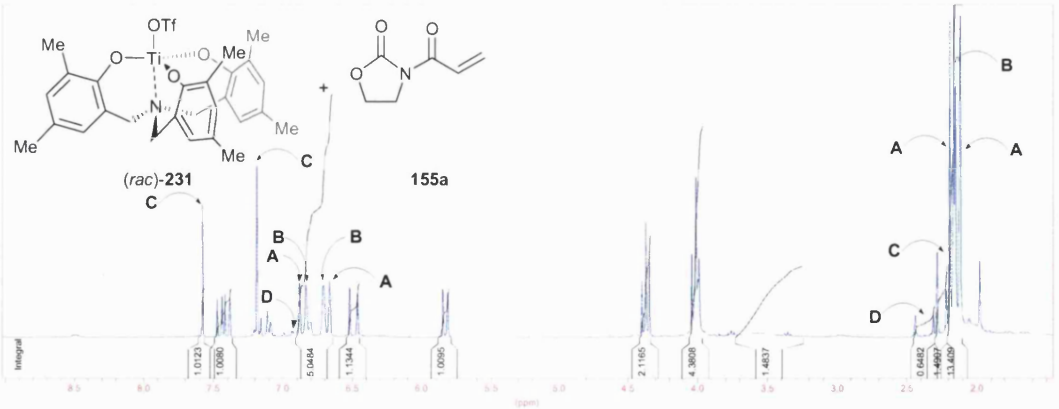
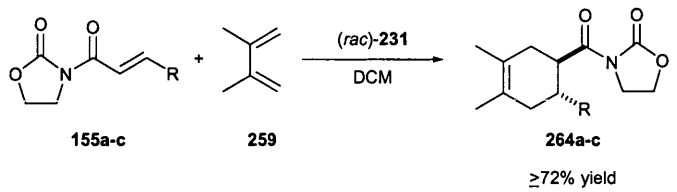



**Figure 99** *$^1$H NMR spectrum of the stoichiometric mixture of **155a** and (rac)-**231***

### 3.6.9 Conventional Diels Alder Reaction between *N*-Acryloyloxazolidin-2-ones 155a-c and 2,3-Dimethyl-1,3-Butadiene 257

The next stage in this investigation was to examine the effect of changing the diene, thus reaction between a representative range of *N*-acryloyloxazolidin-2-ones **155a-c** and 2,3-dimethyl-1,3-butadiene **259** was carried out (Scheme 127, Table 70).




**Scheme 127** *Diels Alder reaction catalysed by (rac)-**231***

**Table 70**

| Entry | Product | R | Catalyst / mol% | Time /h | Conversion /% | Yield /% |
|---|---|---|---|---|---|---|
| 1 | **264a** | H | 20 | 0.5 | 100 | 72 |
| 2 | **264b** | Me | 100 | 3 | 100 | 53 |
| 3 | **264c** | Ph | 100 | 6 | 5 | - |
| 4 | **264c** | Ph | 100 | 24 | 20 | - |

The reactions with 2,3-dimethyl-1,3-butadiene were slower and required longer reaction times and higher catalyst loading than the analogous reactions with cyclopentadiene. The higher reactivity of cyclopentadiene is due to the rigid conformation of the diene which means that it exists exclusively in the s-*cis* conformation necessary for the Diels Alder reaction to occur (Figure 100). 2,3-Dimethyl-butadiene, however, exists in equilibrium between both the s-*cis* and s-*trans* conformations, due to rotation about the central C-C sigma-bond (Figure 100). The most stable conformation is s-*trans* for steric reasons, which is unreactive in the Diels Alder reaction, hence 2,3-dimethyl-1,3-butadiene is less reactive than cyclopentadiene.

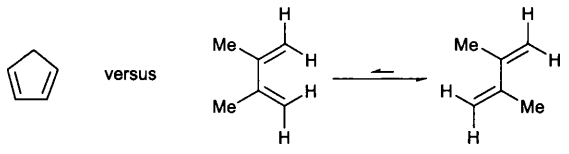


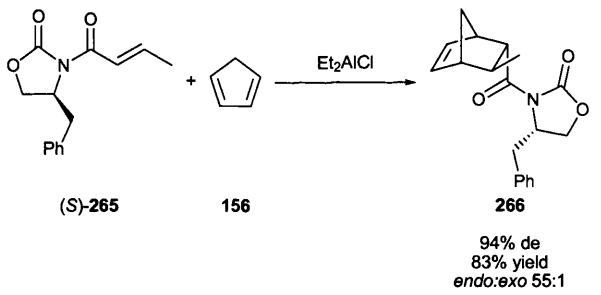

**Figure 100** *Conformations of cyclopentadiene **156** and 2,3-dimethyl-1,3-butadiene **257***

For example, treatment of *N*-acryloyloxazolidin-2-one **155a** and 2,3-dimethyl-1,3-butadiene **257** required 20 mol% of (*rac*)-**231** at high concentration, for the product **264a** to be formed in 100% conversion and 72% isolated yield after 30 minutes (Table

70, entry 1) (the analogous reaction with cyclopentadiene required only 5 mol% of (*rac*)-**231**). Reaction of **155b** with 2,3-dimethyl-1,3-butadiene **259** was found to require one equivalent of (*rac*)-**231** and a reaction time of 3 hours for 100% conversion to **264b** to occur (Table 70, entry 2). However, it was found that reaction of *N*-((*E*)-3-phenyl acryloyl)oxazolidin-2-one **155c** with 2,3-dimethyl-1,3-butadiene **259** and one equivalent of (*rac*)-**231** resulted in only 5% conversion after 6 hours (Table 70, entry 3), compared with 100% conversion in the analogous reaction with cyclopentadiene. Increasing the reaction time to 24 hours resulted in the product in only 20% conversion (Table 70, entry 4).

## 3.7 Chiral Diels Alder Reaction

Due to the good diastereomeric excesses witnessed in the reaction between *N*-acryloyl-oxazolidinones **155a-c** and cyclopentadiene **156**, it was decided to use a chiral dienophile (*S*)-**265** in the hope that a higher diastereoselectivity would be induced. To date this reaction catalysed by a titanium complex has not been reported, but its catalysis by diethyl aluminium chloride has previously been reported by Evans *et al.* (Scheme 128).[158] In this procedure, (*S*)-4-benzyl-*N*-but-2-enoyloxazolidin-2-one **265** was treated with 25 equivalents of cyclopentadiene **156** and 1.4 equivalents of diethyl aluminium chloride for only 5 minutes, to yield (4*S*)-4-benzyl-3-(5-methyl bicyclo[2.2.1]hept-2-enecarbonyl)oxazolidin-2-one **266** in 83% yield and an *endo:exo* ratio of 55:1. The diastereomeric excess of the *endo* product was 94%.



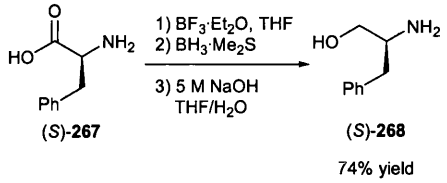

**Scheme 128** *Diels Alder reaction between (S)-4-benzyl-3-but-2-enoyloxazolidin-2-one **265** and cyclopentadiene **156** catalysed by $Et_2AlCl$*

### 3.7.1 Chiral Diels Alder Catalysed by (*rac*)-231

#### Synthesis of (*S*)-4-Benzyloxazolidin-2-one 265

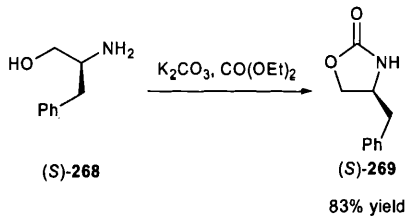
(*S*)-4-Benzyloxazolidin-2-one **265** was synthesised from (*S*)-phenylalanine **267** according to the procedure published by Evans *et al.*[161] Thus, (*S*)-phenylalanine **267** was refluxed with boron trifluoride-etherate, followed by borane dimethyl sulphide

complex and 5 M sodium hydroxide (Scheme 129). This resulted in the formation of (*S*)-2-amino-3-phenylpropan-1-ol **268** in 74% yield. The structure was confirmed by the presence of two chemical shifts at δ = 3.38 and 3.64 ppm in the $^{1}H$ NMR, corresponding to the two protons of the alcoholic methylene group. The $^{13}C$ NMR also revealed the absence of a carbonyl group.




**Scheme 129** *Formation of (S)-2-amino-3-phenylpropan-1-ol* ***268***

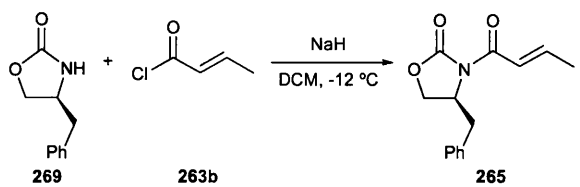
(*S*)-2-Amino-3-phenylpropan-1-ol **268** was then heated with diethyl carbonate and potassium carbonate (Scheme 130). This afforded (*S*)-4-benzyloxazolidin-2-one **269** in 83% yield. The product was identified *via* spectroscopic analysis, the resonances observed for the carbon adjacent to the oxygen were shifted downfield to δ = 4.04 - 4.17 and 4.42 ppm from δ = 3.38 and 3.64 ppm. The $^{13}C$ NMR revealed the presence of a carbonyl carbon with a resonance at δ = 160.0 ppm.




**Scheme 130** *Formation of (S)-4-benzyloxazolidin-2-one* ***269***

### Synthesis of (*S*)-4-Benzyl-3-but-2-enoyloxazolidin-2-one 265

(*S*)-4-Benzyl-*N*-but-2-enoyloxazolidin-2-one **265** was synthesised according to the procedure used for the achiral *N*-acryloyloxazolidin-2-ones **155a-c**. Hence, (*S*)-4-benzyl-oxazolidin-2-one **269** was treated with (*E*)-but-2-enoyl chloride **263b** and sodium hydride in DCM, which resulted in (*S*)-4-benzyl-*N*-but-2-enoyloxazolidin-2-one **265** in 64% yield (Scheme 131).

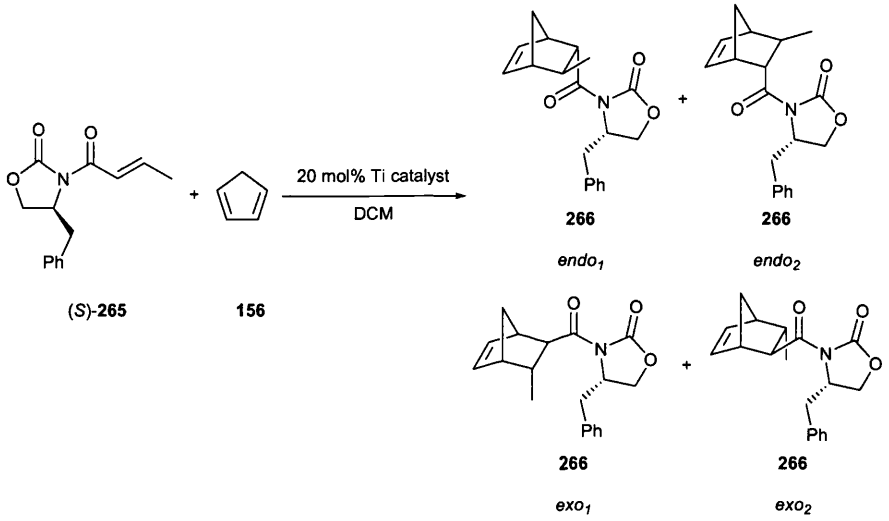



**Scheme 131** *Synthesis of (S)-4-benzyl-3-but-2-enoyloxazolidin-2-one* ***263***

The structure of oxazolidin-2-one **265** was determined *via* spectroscopic analysis. The resonance which is characteristic of the methyl substituent on the alkene was identified at δ = 1.99 ppm. The benzylic protons showed as two doublets of doublets at δ = 2.80 and 3.33 ppm.

### Chiral Diels Alder Reaction Catalysed by Two Titanium complexes

Before using (*rac*)-**231** as a catalyst for the chiral Diels Alder, it was first performed in the presence of chlorotitanium tri-*iso*-propoxide and the titanium complex generated *in situ* from 2,4-dimethylphenol and titanium(IV) chloride; the results from these reactions were then used as a benchmark for comparison (Scheme 132, Table 71).




**Scheme 132** *Diels Alder reaction between (S)-4-benzyl-N-but-2-enoyloxazolidin-2-one **263** and cyclopentadiene **156** catalysed by 20 mol% chlorotitanium tri-iso-propoxide*

**Table 71**

| Entry | Catalyst | Time /h | Yield /% | *endo*:*exo* | *endo*-**266** de /% |
|---|---|---|---|---|---|
| 1 | $TiCl(O^{i}Pr)_3$ | 24 | 84 | 79 : 21 | 96 |
| 2 | $2,4\text{-}Me_2C_6H_3OH$, $TiCl_4$ | 2 | 74 | 72 : 28 | 93 |

The reaction catalysed by 20 mol% of chlorotitanium tri-*iso*-propoxide resulted in the bicyclic product **266** in 84% yield and an *endo*:*exo* ratio of 79:21 (Table 71, entry 1). A total of three diastereomers in a ratio of 77:21:2 (*endo*$_1$:*exo*$_1$:*endo*$_2$) were observed in the $^1$H NMR spectrum and the major product was identified *via* spectroscopic analysis as the *endo* product. Its bicyclic nature was evidenced by the presence of resonances at δ = 2.48 and 3.29 ppm corresponding to the methylene protons on C-7; the bridgehead

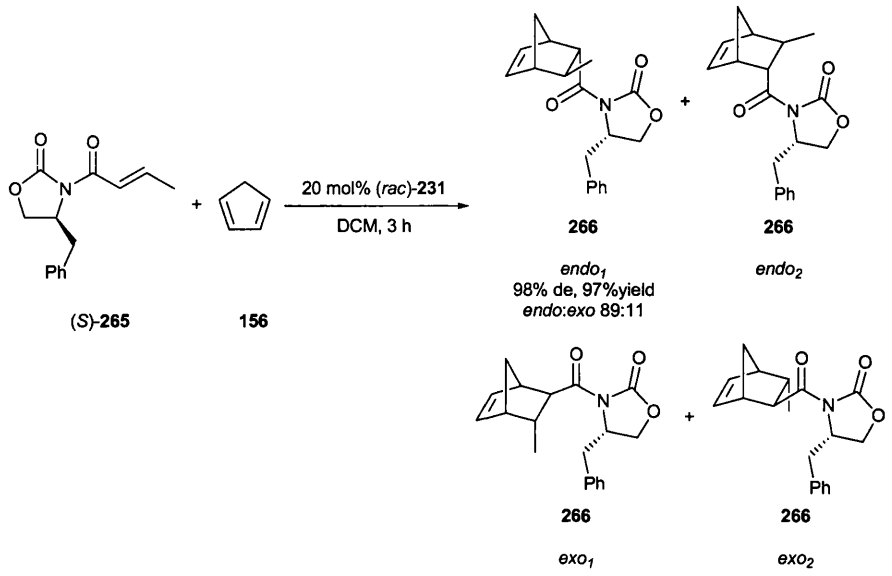
protons were observed at similar resonances as the proton on C-5 and were manifested as multiplets at δ = 1.36-1.41, 1.60-1.67, and 2.02-2.11 ppm. The alkene protons were observed at δ = 5.75 and 6.33 ppm. Spectroscopic analysis of the region of the $^1$H NMR spectrum corresponding to the alkene protons revealed that the major *endo* product was obtained in 96% de.

The use of the titanium complex generated *in situ* by treatment of titanium(IV) chloride with three equivalents of 2,4-dimethylphenol was found to be notably more reactive than chlorotitanium tri-*iso*-propoxide, affording bicyclic product **266** in 74% yield after 2 hours, although with a lower *endo*:*exo* ratio (72:28) (Table 71, entry 2). Interestingly, four diastereomers were observed in the $^1$H NMR spectrum in a ratio of 70:16:2:12 (*endo*$_1$:*exo*$_1$:*endo*$_2$:*exo*$_2$). Analysis of the $^1$H NMR spectrum identified the major product as the *endo* adduct, and analysis of the region corresponding to the revealed the diastereomeric excess of this product was 93%. The presence of the fourth diastereomer, which was assigned as the minor *exo*$_2$ diastereomer, was an interesting observation since it implied that the flexible orientation of the phenolate ligands may have had an effect on the coordination sphere around the titanium, and thus on the diastereoselectivity of the reaction. The reaction also exhibited an inversion of selectivity between the minor *exo*$_2$ and *endo*$_2$ diastereomers, when compared to the reaction catalysed by chlorotitanium tri-*iso*-propoxide, since the *endo*$_2$:*exo*$_2$ ratio of the minor diastereomers was 17:83 in favour of the *exo* diastereomer which had not been detected in the previous reaction. It was hoped that the rigid phenolate system of (*rac*)-**231** would improve the diastereoselectivity of this reaction even further.

#### Chiral Diels Alder Reaction Catalysed by (*rac*)-231

It was found that treatment of (*S*)-4-benzyl-*N*-but-2-enoyloxazolidin-2-one **265** with cyclopentadiene **156** and 20 mol% (*rac*)-**231**, resulted in the bicyclic product **266** in an excellent 97% yield after 3 hours (Scheme 133). Analysis of the $^1$H NMR spectrum revealed that the major product had been obtained in an improved *endo*:*exo* ratio of 89:11. Only three diastereomers were observed in a ratio of 88:11:1 (*endo*$_1$:*exo*$_1$:*endo*$_2$), which indicated that there was an improved interaction between the rigid phenolate framework of (*rac*)-**231** and the titanium's coordination sphere when compared to the tris(2,4-dimethyl phenolate) titanium complex formed *in situ* ((Table 71, entry 2). Analysis of the $^1$H NMR region corresponding to the alkene protons confirmed that the

major product was the *endo* adduct and that its diastereomeric excess was 98%, proving to be more selective than the reaction catalysed by chlorotitanium tri-*iso*-propoxide.




**Scheme 133** *Diels Alder reaction between (S)-4-benzyl-N-but-2-enoyloxazolidin-2-one* ***265*** *and cyclopentadiene* ***156*** *catalysed by 20 mol% (rac)-****231***

### 3.7.2 NMR Studies

An NMR experiment was performed with a stoichiometric mixture of chiral oxazolidin-2-one **265** and (*rac*)-**231** (Appendix 1, Figure 101, Figure 102, Figure 103). In accordance with the experiment with dienophile **155a**, this revealed a mixture of four possible species (**A-D**) including a coordinated complex (**A**) and an uncoordinated complex (**B**). This is evidenced by the presence of two peaks relating to the aryl methyl groups of the coordinated complex (**A**) at $\delta$ = 2.12 and 2.19 ppm and two peaks corresponding to the uncoordinated species at $\delta$ = 2.14 and 2.18 ppm. Four signals were also observed for the aromatic protons of the ligand, $\delta$ = 6.67 and 6.89 ppm for the coordinated species (**A**) and $\delta$ = 6.70 and 6.82 ppm for the uncoordinated complex (**B**). Another species (**C**) also appeared to be represented by a resolved doublet at $\delta$ = 4.01 ppm representing its benzylic protons, two singlets at $\delta$ = 2.20 and 2.28 ppm corresponding to the aryl methyl groups, and $\delta$ = 7.20 and 7.60 ppm corresponding to the aryl protons. A further species (**D**) appears to be represented by two singlets at $\delta$ = 2.30 and 2.43 ppm corresponding to the aryl methyl groups, and $\delta$ = 6.91 and 7.00 ppm corresponding to the aryl protons. The presence of these species may be due to the

degradation of the catalyst. It was found that the signals corresponding to **265** were once again unmoved.

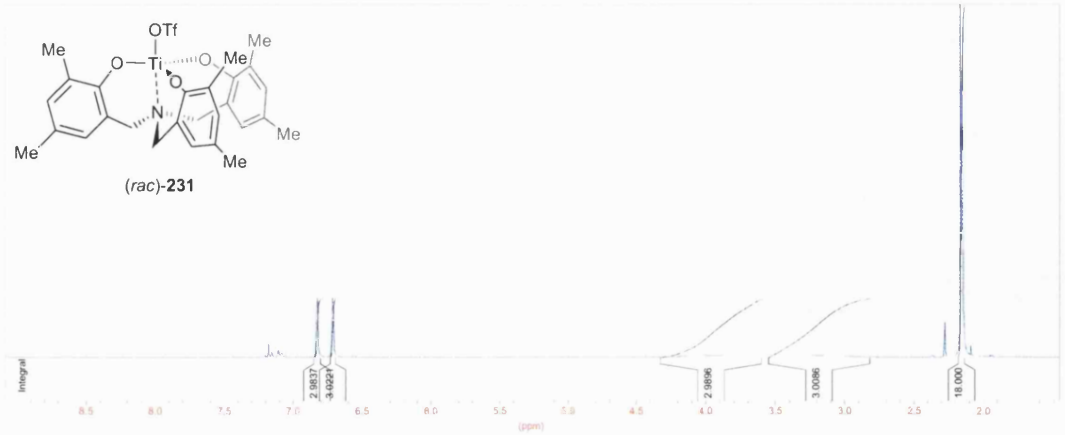



**Figure 101** *$^1$H NMR spectrum of complex (rac)-**231***

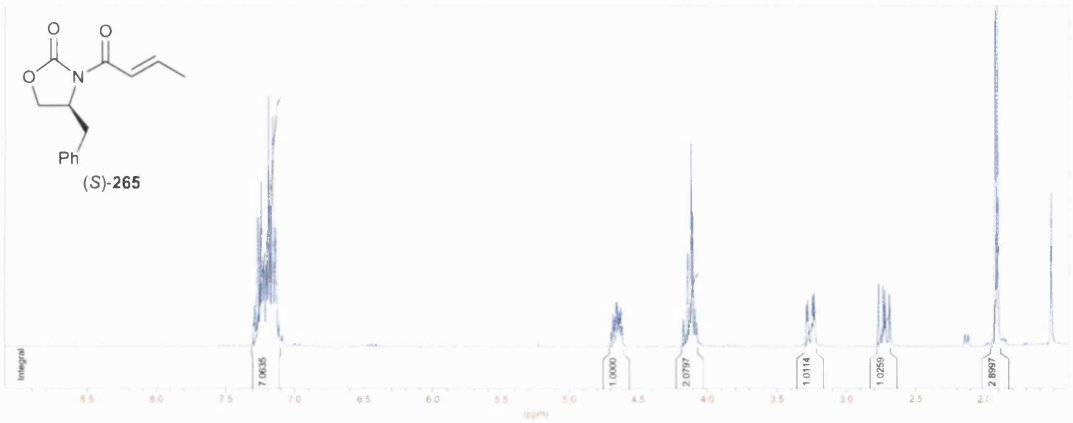



**Figure 102** *$^1$H NMR spectrum of chiral oxazolidin-2-one **265***

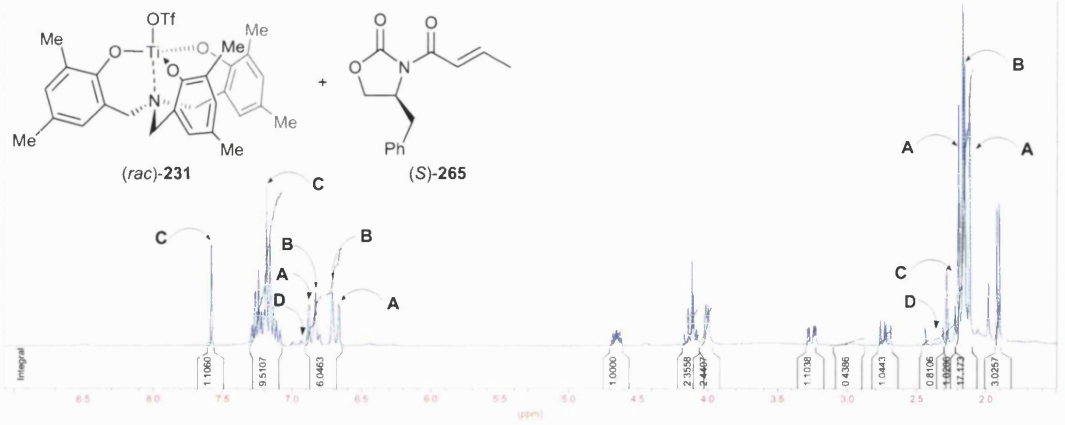
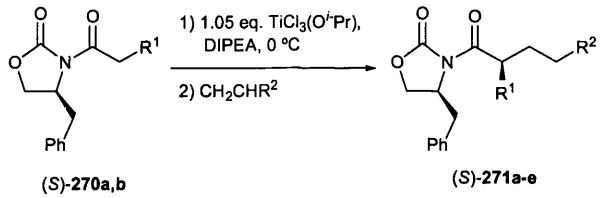



**Figure 103** *$^1$H NMR spectrum of the stoichiometric mixture of chiral oxazolidin-2-one (S)-**265** and (rac)-**231***

The Lewis acidity of the complex being satisfied, the next goal was to determine whether synthetically useful protocols could be devised using titanium enolates of (*rac*)-**231**. The first reaction examined for this purpose was the Michael addition.

## 3.8 Michael Addition

In 1991, Evans *et al.* reported the use of titanium enolates, derived from analogues of *N*-propionyl oxazolidin-2-one, in the Michael addition to a range of electrophilic alkenes.[162] The titanium enolates were formed *in situ* by treatment of the relevant oxazolidin-2-one with chlorotitanium(IV) *iso*-propoxide and di-*iso*-propylethylamine (DIPEA) in DCM at 0 °C followed by addition of the electrophilic alkene. This resulted in the corresponding adducts **271a-e** being formed in high yields (70-93%) with good diastereoselectivity (90-99%) (Scheme 134, Table 72). For example, treatment of the titanium enolate of (*S*)-4-benzyl-3-propionyloxazolidin-2-one **270a** with acrylonitrile afforded (*R*)-5-((*S*)-4-benzyl-2-oxazolidin-3-yl)-4-methyl-5-oxopentanenitrile **271a** in 96% de and 93% yield (Table 72, entry 1).




**Scheme 134** *Michael Addition catalysed by chlorotitanium(IV) iso-propoxide*

**Table 72**

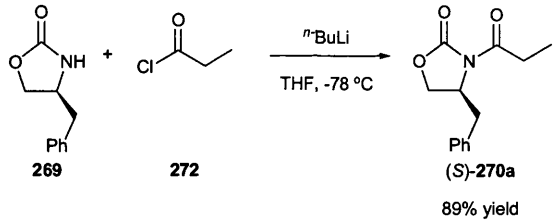
| Entry | Product | $R^1$ | $R^2$ | Yield /% | de /% |
|---|---|---|---|---|---|
| 1 | **271a** | Me | CN | 93 | 96 |
| 2 | **271b** | Me | $CO_2Me$ | 78 | 98 |
| 3 | **271c** | Me | $CO_2{}^tBu$ | 79 | 90 |
| 4 | **271d** | $(CH_2)_2CO_2Me$ | CN | 70 | 99 |
| 5 | **271e** | $CHMe_2$ | CN | 84 | 99 |

### 3.8.1 Michael Addition Catalysed by (*rac*)-231

#### Synthesis of (*S*)-4-benzyl-3-propionyloxazolidin-2-one 270a

(*S*)-4-Benzyl-3-propionyloxazolidin-2-one **270a** was synthesised following the procedure published by Evans *et al.*[161] Thus, (*S*)-4-benzyl-oxazolidin-2-one **269** was treated with $^n$butyl lithium and propionyl chloride **272** in THF (Scheme 135). This

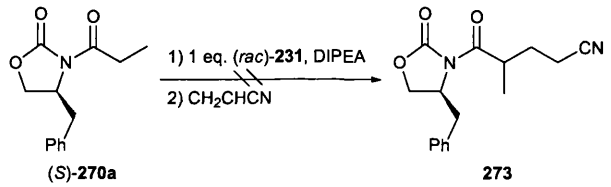
resulted in (*S*)-**270** in 89% yield as a colourless crystalline solid. Its structure was confirmed by comparison of its $^1$H NMR data to the literature.[161]




**Scheme 135** *Synthesis of (S)-4-Benzyl-3-propionyloxazolidin-2-one* ***270a***

### Michael Addition Catalysed by (*rac*)-231

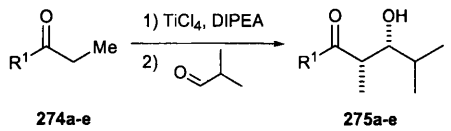
Following the procedure published by Evans *et al.*[162] an attempt was made to react the titanium enolate of (*S*)-4-benzyl-3-propionyloxazolidin-2-one **270a**, generated *via* treatment with (*rac*)-**231** and DIPEA, with acrylonitrile (Scheme 136). Unfortunately, after a reaction time of 45 hours, only the starting material was obtained, with no trace of any of the desired product observed in the $^1$H NMR spectra of the reaction mixture.




**Scheme 136** *Attempted Michael addition to (S)-4-benzyl-3-propionyloxazolidin-2-one catalysed by (rac)-****231***

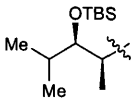
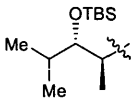
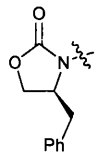
## 3.9 Aldol Reaction

In 1991, Evans *et al.* reported the asymmetric aldol reaction of a range of titanium enolates.[163] These enolates were generated *in situ* by treatment with titanium(IV) chloride and DIPEA. This was followed by addition of *iso*-butyraldehyde, which resulted in the corresponding β-hydroxy aldehydes **275a-e** in high yields and good diastereoselectivities (88-92%) (Scheme 137, Table 73), which are comparable to those obtained when using boron enolates.[164] For example, addition of *iso*-butyraldehyde to the titanium enolate of pentan-3-one **274a**, resulted in 5-hydroxy-4,6-dimethylheptan-3-one **275a** in 84% de and 95% yield (Table 73, entry 1).

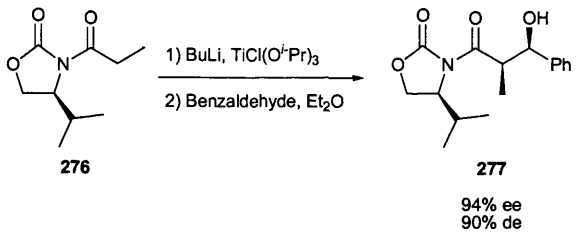



**Scheme 137** *Diastereoselective aldol reactions of a range of titanium enolates*

**Table 73**

| Entry | Product | $R^1$ | Yield /% | de /% |
|---|---|---|---|---|
| 1 | **275a** | $CH_2Me$ | 95 | 84 |
| 2 | **275b** | $CH_2(CH_3)_2$ | 95 | 86 |
| 3 | **275c** |  | 96 | 92 |
| 4 | **275d** |  | 82 | 90 |
| 5 | **275e** |  | 87 | 88 |

In the same year, Thornton *et al.* reported aldol reactions of the titanium enolate of (*S*)-*N*-propionyl-4-isopropyloxazolidin-2-one **276** and benzaldehyde **116**, which showed a reversal of selectivity when compared with the products obtained using a boron enolate (and those obtained by Evans *et al.*).[165] The titanium enolate was formed *via* transmetallation of the lithium enolate by treatment with an excess of chlorotitanium tri-*iso*-propoxide. Subsequent addition of benzaldehyde resulted in a 'non-Evans' *syn* aldol adduct in high diastereoselectivity and enantiomeric excess. The nature of the solvent was found to have an effect on the enantio- and diastereoselectivities, with the best results being obtained when the reaction was performed in diethyl ether, resulting in β-hydroxy *N*-acyl-oxazolidin-2-one **277** in 90% de and 94% ee (Scheme 138).




**276** **277**

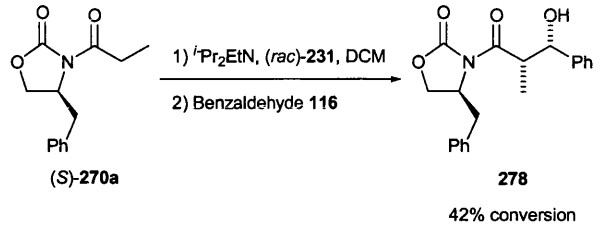
94% ee
90% de

**Scheme 138** *Reaction of the titanium enolate of (S)-N-propionyl-4-isopropyloxazolidin-2-one* ***276*** *and benzaldehyde* ***116***

### 3.9.1 Aldol Reaction catalysed by (*rac*)-231

Despite the failure of the Michael addition, it was decided to attempt the aldol reaction of the titanium enolate of (*S*)-**235** generated *via* treatment of (*S*)-4-benzyl-3-propionyl-oxazolidin-2-one **270a** with DIPEA and one equivalent of (*rac*)-**231** (Scheme 139) following the procedure reported by Evans *et al.*[163] After 24 hours the *syn*-product was

obtained in 42% conversion. This was identified by comparison of the $^1$H NMR data with the literature and was evidenced by the presence of a doublet at $\delta$ = 5.25 ppm corresponding to the methylene group attached to the alcohol, along with the broad singlet at $\delta$ = 3.08 ppm representing the alcoholic proton. A resonance manifested as a multiplet relating to the newly formed methine group adjacent to the carbonyl was observed at $\delta$ = 4.01-4.11 ppm.




**Scheme 139** *Aldol reaction catalysed by (rac)-**231***

This preliminary result was very encouraging as it confirmed that the titanium enolate formed from (*rac*)-**231** was reactive with electrophiles. This investigation is being continued by another member of the SDB group.

## 3.10 Conclusion

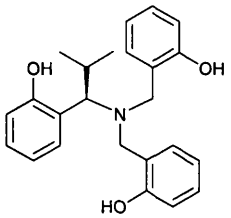
Titanium triflate complex (*rac*)-**231** has been shown to be an effective Lewis acid catalyst for a range of organic transformations. The preliminary investigations into the reaction of the titanium enolates derived from (*rac*)-**231** were also found to be positive. The $C_3$-symmetric structure has also been shown to have an affect on the diastereoselectivity of the chiral Diels Alder reaction indicating that a chiral analogue of (*rac*)-**231** may have the potential to induce a high degree of chirality into organic asymmetric transformations. It was therefore decided to attempt to synthesise a chiral triphenolate ligand in the hope that this would induce a higher diastereoselectivity.

# CHAPTER 4:
# *Attempts Towards a Chiral Ligand Synthesis*

# 4 ATTEMPTS TOWARDS A CHIRAL LIGAND SYNTHESIS

## 4.1 Aims and Objectives

The aim of this chapter was to synthesise a *pseudo*-$C_3$-symmetric chiral analogue of complex (*rac*)-**231**, based on ligand (*R*)-**279** (Figure 104). Preliminary work focussed on the synthesis of ligand (*R*)-**279**, due to the commercial availability of potential starting materials. An *iso*-propyl group was chosen for this ligand in order to ensure that it was sterically demanding enough to control the propeller-type chirality of the ensuing metal complex. It would also results in a more diagnostic $^1$H NMR spectrum than a *tert*-butyl group, with the resonances corresponding to the two methyl groups appearing as two doublets, whereas those representing a *tert*-butyl group would be seen as a singlet.

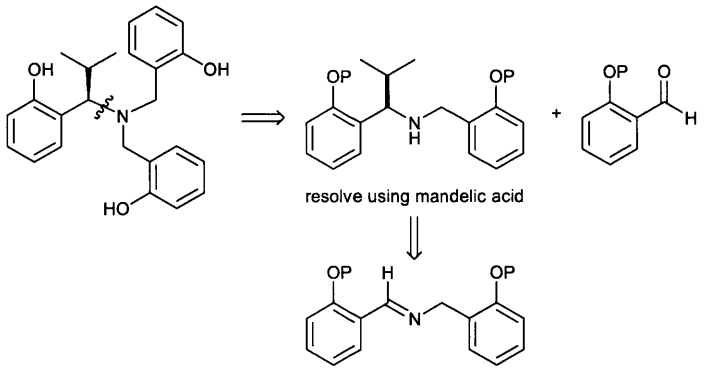


(*R*)-**279**

**Figure 104** *Ligand (R)-**279***

## 4.2 Synthesis of Ligand (*R*)-279 – A Resolution Approach

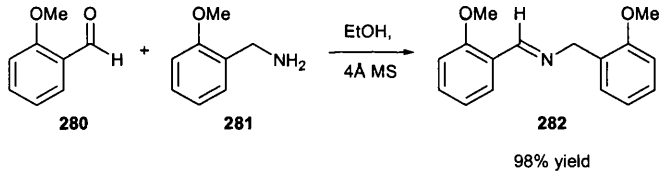
There are several approaches to the synthesis of ligand (*R*)-**279**, the most facile was thought to be a resolution approach involving the preparation of a racemic secondary amine which could then be resolved using mandelic acid according to a literature precedent for this class of secondary amines (Scheme 140).[166] This amine could then be taken on to form the tertiary amine *via* a reductive amination reaction. The secondary amine would be formed *via* addition of an alkyl group to an imine. This method was envisaged to be a quick and efficient synthesis to both the chiral and racemic forms of the ligand.




**Scheme 140** *Retro-synthesis of ligand (R)-**279***

## 4.2.1 Synthesis of Imine 282

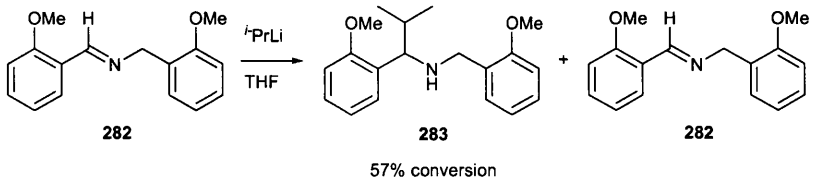
A methoxy group was chosen as the phenolic protecting group due to the commercial availability of the starting materials. Thus, imine **282** was formed *via* treatment of 2-methoxybenzaldehyde **280** with 2-methoxy-benzylamine **281** in ethanol in the presence of 4Å molecular sieves (Scheme 141). This resulted in *N*-(2-methoxy-benzylidene)(2-methoxyphenyl)methanamine **282** in a 98% yield after 26 hours. The structure was confirmed by $^1$H NMR analysis which showed a peak corresponding to the imine proton at $\delta$ = 8.89 ppm. The benzylic protons were observed at $\delta$ = 4.85 ppm, compared with $\delta$ = 3.81 ppm for 2-methoxybenzylamine.




**Scheme 141** *Synthesis of imine **282***

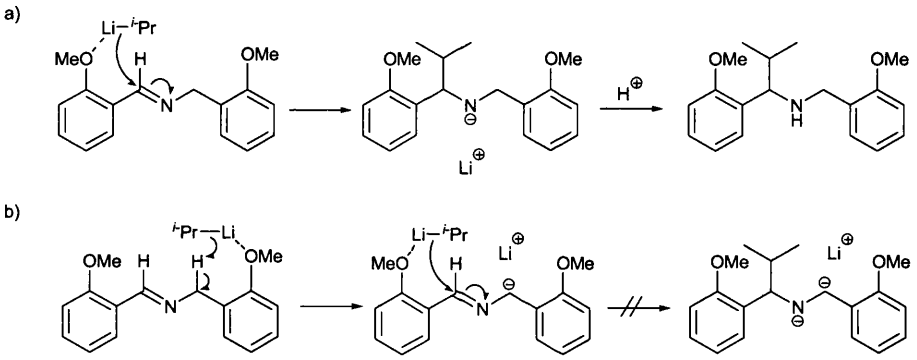
## 4.2.2 Addition to Imine 282

It was decided to use *iso*-propyl lithium to introduce the alkyl group to the secondary amine. Thus, imine **282** was treated with *iso*-propyl lithium at -78 °C in THF (Scheme 142). After being stirred at this temperature for six hours the reaction mixture was allowed to warm to room temperature and stirred overnight. An aqueous work up with ammonium chloride resulted in a mixture of starting material **282** and amine **283**. Unfortunately, the reaction was found to only have proceeded to 57% conversion, whilst when an excess of *iso*-propyl lithium was used in an attempt to drive the reaction to completion, the conversion was still only 62%.




**Scheme 142** *Addition of iso-propyl lithium to imine* ***282***

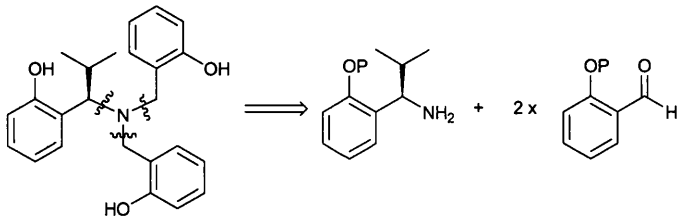
It is likely that this addition reaction proceeds *via* coordination of the *iso*-propyl lithium counterion to the oxygen lone pair of the methoxy group which then directs the delivery of the *iso*-propyl group to the imine functionality (Scheme 143, pathway a). However, the *iso*-propyl lithium may also act as a base, deprotonating the imine at the benzylic position instigated by coordination of the *iso*-propyl lithium to the lone pair of the other methoxy group. This would result in further addition of *iso*-propyl lithium to the imine becoming disfavoured, as it would afford a high-energy intermediate containing two negative charges being in close proximity to one another (Scheme 143, pathway b).




**Scheme 143** *Mechanistic considerations in the addition of iso-propyl lithium to imine* ***282***

## 4.3 Synthesis of Ligand (*R*)-279 – A Reductive Amination Approach

A second retro-synthetic analysis of ligand (*R*)-**279** revealed that it could be formed *via* the reductive amination of a chiral amine with two equivalents of protected 2-hydroxybenzaldehyde (Scheme 144). This synthetic route has the advantage over the previous one, in that the use of a chiral amine negates the need to resolve any of the products.

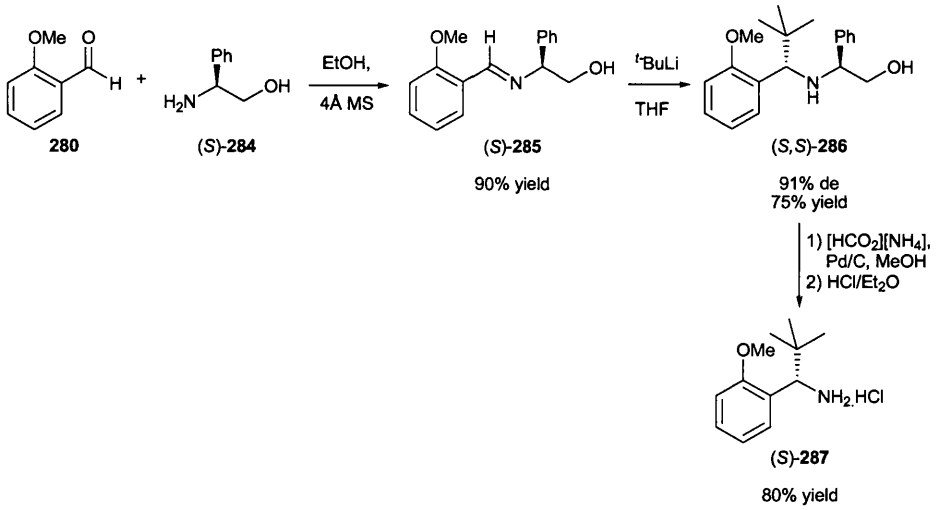



**Scheme 144** *A second retro-synthesis of ligand (R)-**279***

### 4.3.1 Literature Precedence

In 2000, Kündig *et al.* reported the synthesis of chiral amines using (*S*)- and (*R*)-2-amino-2-phenylethanol **284** as a chiral auxiliary.[167] This involved the formation of imine (*S*)-**285** from (*S*)-2-amino-2-phenylethanol **284** and 2-methoxybenzaldehyde **280**, followed by the addition of *tert*-butyl lithium at -85 °C to yield (*S,S*)-**286** in 91% de and 75% yield after chromatography (Scheme 145). This was then deprotected using palladium on carbon and ammonium formate to afford amine (*S*)-**287** in 80% yield.

This synthesis appeared to be an efficient synthesis of chiral primary amines of the type required for the synthesis of ligand **279** and so this procedure was followed for the synthesis of the parent chiral amine of ligand **279**.

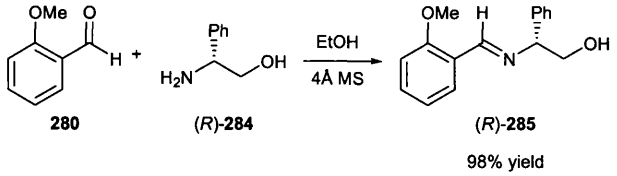



**Scheme 145** *Using (S)-2-amino-2-phenylethanol **284** as a chiral auxiliary*

### 4.3.2 Synthesis of Imine (*R*)-285

Imine (*R*)-**285** was synthesised following the procedure published by Kündig *et al.*[168] Thus, 2-methoxybenzaldehyde **280** was stirred with (*R*)-2-amino-2-phenylethanol **284** in ethanol in the presence of 4Å molecular sieves, to yield (*R*)-2-(2-methoxy benzylideneamino)-2-phenylethanol **285**, in 98% yield (Scheme 146). The structure

was confirmed by the comparison of the $^1$H NMR spectra to the literature.[168] A resonance corresponding to the imine proton was observed at $\delta$ = 9.08 ppm.



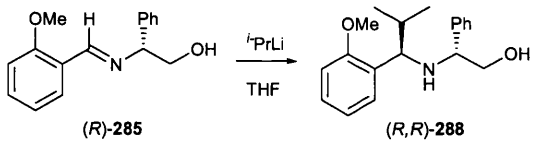

280 (*R*)-284 (*R*)-285

98% yield

**Scheme 146** *Formation of imine (R)-**285***

### 4.3.3 Addition to Imine (*R*)-285

For the reasons mentioned earlier, *iso*-propyl lithium was used for the addition to imine (*R*)-**285**. Thus, a solution of imine (*R*)-**285** in THF solidified in liquid nitrogen was treated with two equivalents of *iso*-propyl lithium and then stirred at -85 °C for 6 hours (Scheme 147). This resulted in (*R*)-2-((*R*)-1-(2-methoxyphenyl)-2-methylpropylamino) -2-phenylethanol **288** in 94% de and 83% yield. Column chromatography improved the diastereomeric excess to 96%, but the yield was decreased to 57%. The structure of the product was confirmed by $^1$H NMR spectroscopic analysis, which indicated the presence of the *iso*-propyl group by two doublets at $\delta$ = 0.64 and 1.05 ppm corresponding to the methyl groups, and a multiplet at $\delta$ = 1.96 ppm which relates to the proton of the tertiary carbon. It is noteworthy that the two diastereotopic methyl groups are split by 0.4 ppm indicating a relatively rigid structure in which one of the methyl groups is shielded by the anisotropic effect of one of the aryl groups.




(*R*)-285 (*R,R*)-288

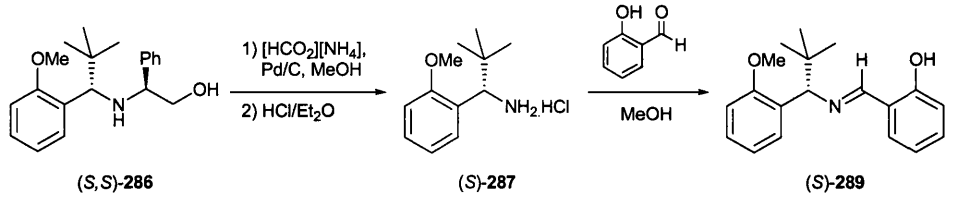
94% de
83% yield

**Scheme 147** *Addition of iso-propyl lithium to imine (R,R)-**285***

It is interesting to note that when the reaction was repeated at -78 °C for a longer period of time, in the hope of improving the diastereoselectivity of the reaction, the diastereomeric excess was found to be a disappointing 85% de.

The absolute configuration of amine **288** was assigned as (*R,R*) by analogy with the configuration of amine (*S,S*)-**286** obtained using (*S*)-2-amino-2-phenylethanol by Kündig *et al.*[168] which was assigned according to the Salicylideneamine Chirality Rule.[169] This rule is used to predict the absolute stereochemistry of chiral primary

amines by CD spectroscopic analysis of their imines formed with 2-hydroxybenzaldehyde. For example, Kundig *et al.* used CD spectroscopic analysis of imine **289**, formed by the condensation of deprotected amine (*S*)-**287** and 2-hydroxybenzaldehyde, to determine its absolute configuration as *S* (Scheme 148).

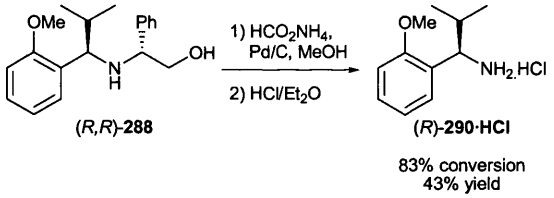



**Scheme 148** *Formation of imine (S)-**289** for CD spectroscopy*

## 4.3.4 Deprotection of Amine (*R,R*)-288

### Hydrogenation Method

The removal of the chiral auxiliary was first attempted following the procedure published by Kündig *et al. via* hydrogenation.[168] Amine (*R,R*)-**288** was therefore, treated with palladium on carbon and ammonium formate in refluxing methanol (Scheme 149). The first time this was attempted, product (*R*)-**290·HCl** was obtained in 83% conversion and 43% yield, which was confirmed by spectroscopic analysis. The resonances corresponding to the methyl groups of the *iso*-propyl were shown to have shifted to $\delta = 0.72$ and 1.04 ppm.




**Scheme 149** *Deprotection of amine (R,R)-**288** via hydrogenation*

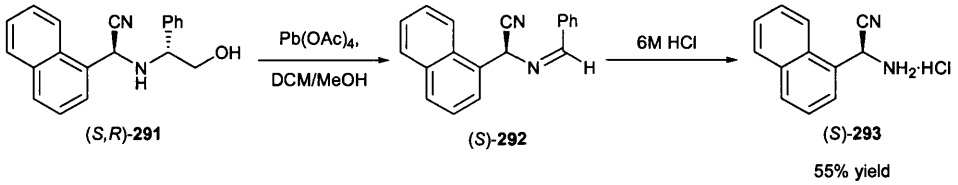
However, when this reaction was repeated on a range of scales the results were erratic as shown in Table 74, and it soon became clear that this was an unreliable method for the deprotection of amine (*R,R*)-**288** in this synthesis.

**Table 74**

| Entry | Time /h | Conversion /% | Yield /% |
|---|---|---|---|
| 1 | 2 | 83 | 43 |
| 2 | 2 | 60 | 28 |
| 3 | 10 | 18 | - |

### Oxidative Cleavage Method

A literature search revealed that oxidative cleavage using lead(IV) acetate was an efficient and effective method for the deprotection of α-amino alcohols.[170,171] For example, Hosangadi *et al.* reported the removal of the 2-phenyl ethanol auxiliary fragment from amine (*S,R*)-**291** using lead(IV) acetate.[170] Treatment of amine (*S,R*)-**291** with lead(IV) acetate for five minutes, lead to the formation of imine (*S*)-**292**, which in turn was hydrolysed, without further purification, with 6 M hydrochloric acid to yield (*S*)-2-amino-2-(naphthalen-1-yl)acetonitrile hydrochloride **293** in 55% yield (Scheme 150).

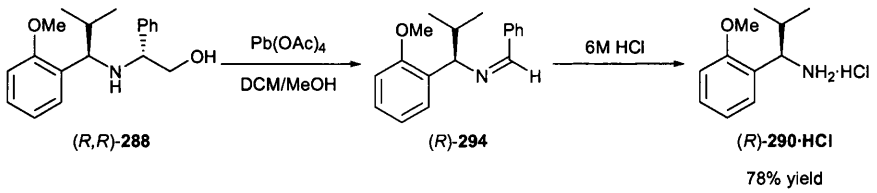



(*S,R*)-**291** (*S*)-**292** (*S*)-**293**

55% yield

**Scheme 150** *Deprotection of (S,R)-**291** using lead(IV) acetate*

Thus, amine (*R,R*)-**288** was deprotected following this procedure *via* treatment with lead(IV) acetate resulting in the formation of imine (*R*)-**294**, which was isolated in 96% yield (Scheme 151). Its structure was confirmed *via* spectroscopic analysis which showed the absence of the methylene group and the presence of the imine proton at δ = 8.24 ppm. Imine (*R*)-**294** was converted to amine (*R*)-**290·HCl** without further purification, *via* hydrolysis with 6M hydrochloric acid to yield (*R*)-1-(2-methoxyphenyl)-2-methyl propan-1-amine hydrochloride **290·HCl** in 78% yield (Scheme 151). $^1$H NMR spectroscopy confirmed the formation of amine (*R*)-**290·HCl** which was evidenced by the absence of the imine peak. The two methyl groups of the *iso*-propyl unit were still found to be non-equivalent with doublets at δ = 0.72 and 1.04 ppm.

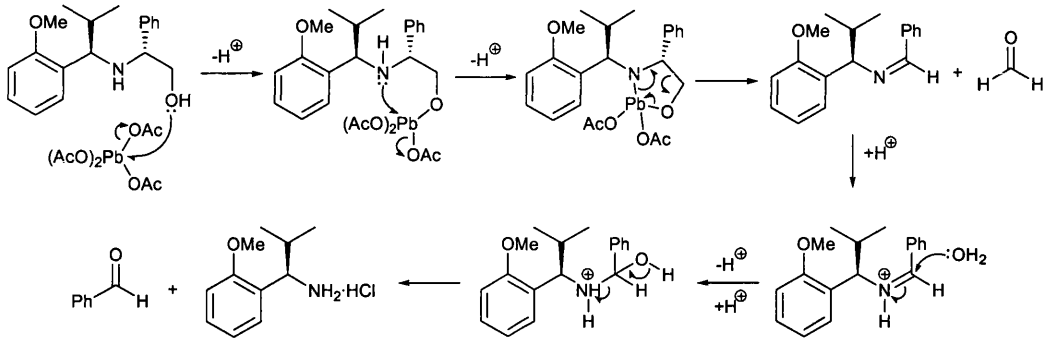



(*R,R*)-**288** (*R*)-**294** (*R*)-**290·HCl**

78% yield

**Scheme 151** *Deprotection of amine (R,R)-**288** using lead(IV) acetate*

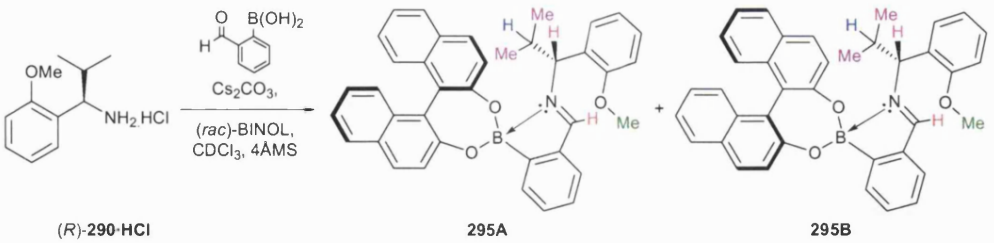
The mechanism of the oxidative cleavage of α-amino alcohols with lead(IV) acetate is similar to that of 1,2-diols. Lead(IV) acetate is chelated by the α-amino alcohol forming a cyclic intermediate which then undergoes elimination to afford the desired imine and formaldehyde (Scheme 152). Standard acid hydrolysis of the resulting imine with 6M hydrochloric acid then affords the amine hydrochloride salt and benzaldehyde.



**Scheme 152** *Mechanism of the oxidative cleavage of α-amino alcohol (R,R)-**288** with lead(IV) acetate*

### 4.3.5 Determination of Enantiomeric Excess of Primary Amine (*R*)-290

The enantiomeric excess of the primary amine was then determined *via* a three component self assembly system which has been developed within the Bull Group as a versatile alternative to Mosher's amide derivatisation. Treatment of amine hydrochloride (*R*)-**290·HCl** with caesium carbonate, 2-formylboronic acid, and chiral BINOL in deuterated chloroform results in the formation of two diastereomers **A** and **B** of chiral imine **295** with a rigid structure. A complex was first formed *via* mixing amine (*R*)-**290·HCl** with racemic BINOL in order to determine the chemical shifts of both diastereomers as an alternative to preparing an authentic sample of racemic amine. As depicted in Figure 105, a number of resonances corresponding to the colour-coded functional groups of **295A** and **295B** were fully resolved for each diastereomeric complex (Scheme 153). For example, the two methyl groups are observed at $\delta = 0.62$ and 1.64 ppm and at $\delta = 0.80$ and 0.96 ppm for diastereomers **A** and **B** respectively; the resonance corresponding to the methoxy group in **A** is seen at $\delta = 3.00$ ppm, whilst the same peak is observed at $\delta = 3.39$ ppm in diastereomer **B**. Thus, the two diastereomers can be distinguished in the $^1$H NMR which, when chiral BINOL is used, enables the diastereomeric excess of the imine to be determined, hence inferring the enantiomeric excess of amine (*R*)-**290·HCl**.




**Scheme 153** *Determination of the enantiomeric excess of amine **290·HCl** with (rac)-BINOL*

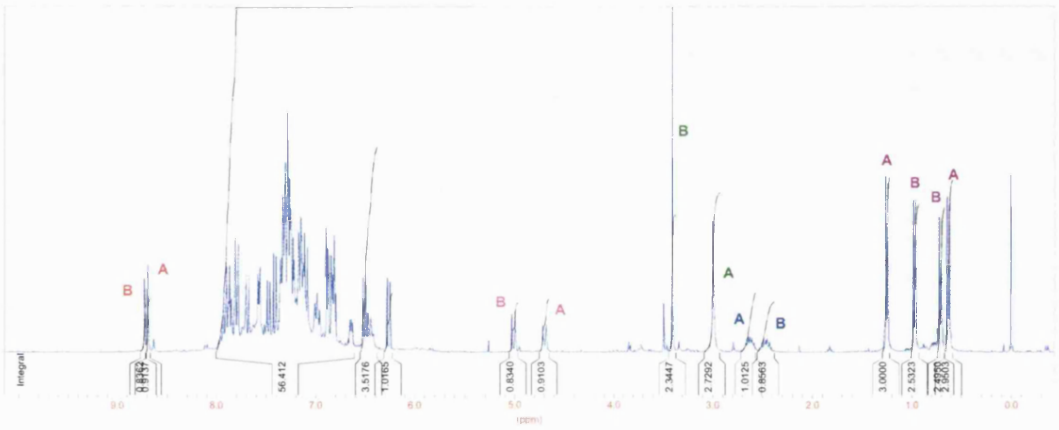
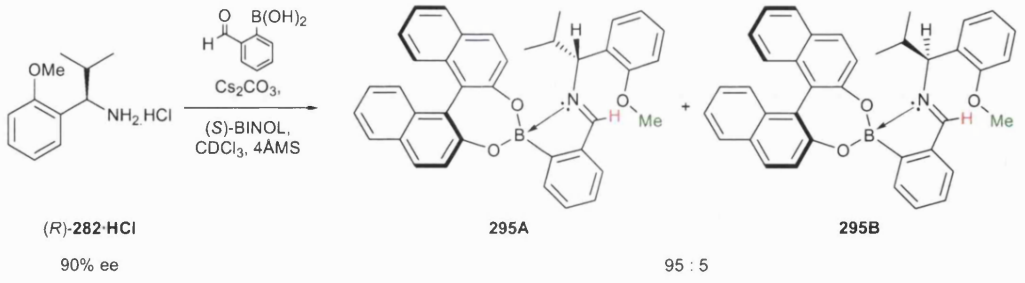



**Figure 105** *$^1$H NMR ($CDCl_3$) of the racemic mixture of **295A** and **295B***

Thus, chiral amine (*R*)-**290·HCl** was treated with caesium carbonate, 2-formylboronic acid, and enantiopure (*S*)-BINOL in deuterated chloroform, which resulted in **295A** as the major diastereomer (Scheme 154). Examination of the $^1$H spectra confirmed that diastereomer **A** was predominant and had been formed in 90% ee. For example, analysis of the integrals in the region corresponding to the methoxy peaks (**A**: δ = 3.00 ppm; **B**: δ = 3.39 ppm), the diastereomeric excess of the imine, and thus the enantiomeric excess of the amine, was revealed to be 90% (Figure 106).




**Scheme 154** *Determination of the enantiomeric excess of amine (R)-**290·HCl** with (S)-BINOL*

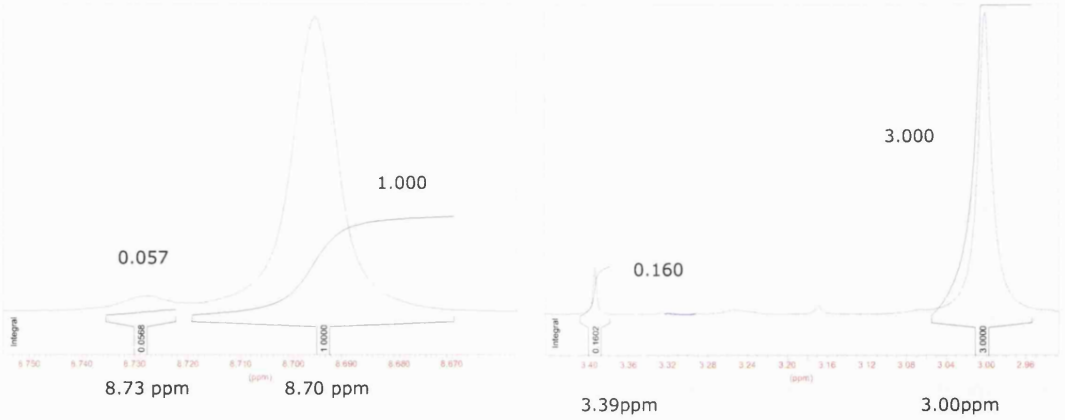
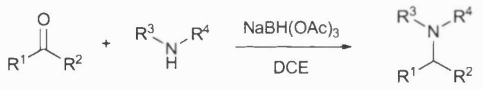



**Figure 106** *Analysis of two regions of the $^1H$ NMR spectrum ($CDCl_3$) of complexes **295A** and **295B**, referring to the imine and methoxy peaks (left and right respectively)*

The subsequent reactions performed on chiral products derived from amine (*R*)-**290·HCl** are unlikely to cause racemisation of the benzylic stereocentre, meaning that they should be produced in 90% ee.

### 4.3.6 Reductive Amination of Amine (*R*)-290·HCl

In 1996, Abdel-Magid *et al.* reported the direct reductive amination of a wide range of aldehydes and ketones with sodium triacetoxyborohydride.[172] The authors found that this method resulted in the amine products in good yields and with fewer side products than with sodium cyanoborohydride as the reductant. This method was applied to both primary and secondary amines; the reaction rate was found to be increased by the addition of acetic acid, although this was found to be unnecessary for the reactions of aldehydes. A representative range of reactions is shown in Scheme 155 and Table 75.

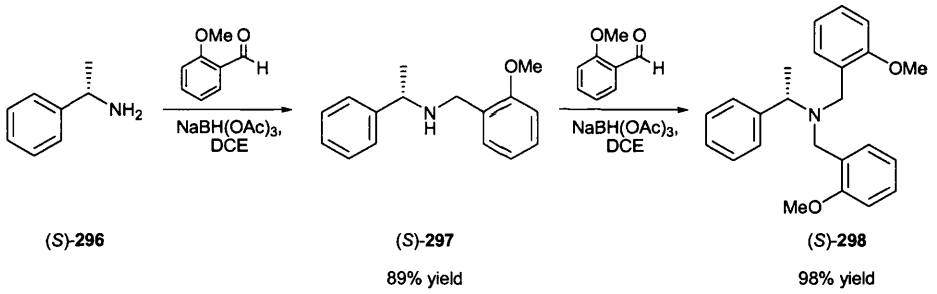



**Scheme 155** *The reductive amination of aldehydes and ketones mediated by sodium triacetoxy borohydride*

**Table 75**

| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Time | Yield /% |
|---|---|---|---|---|---|---|
| 1 | Ph | Me | Bn | H | 10 d | 55 |
| 2 | $^c$hexyl | H | Bn | H | 1 h | 98 |
| 3 | 3-MeO($C_6H_4$) | H | Ph | H | 24 h | 88 |
| 4 | 3-$NO_2$($C_6H_4$) | H | -($CH_2$)$_4$CH($CO_2$Et)- | | 1.5 h | 96 |

It was decided to optimise a reductive amination protocol on a model system of α-methylbenzylamine and 2-methoxybenzaldehyde, before using the precious chiral amine (*R*)-**290·HCl** in this transformation. Thus, a solution of (*S*)-α-methylbenzylamine **296** in DCE was treated with 2-methoxybenzaldehyde and sodium triacetoxy borohydride at room temperature for 24 hours, after which secondary amine (*S*)-**297** was obtained in 89% yield (Scheme 156). It was noted that there was a small amount of tertiary amine (*S*)-**298** present in the crude product. The structure of secondary amine (*S*)-**297** was identified by $^1$H NMR spectroscopic analysis, which revealed the absence of a resonance corresponding to the aldehyde, the presence of two resonances relating to the diastereotopic protons of the benzylic methylene group (δ = 3.49 and 3.66 ppm), and a singlet ascribed to the methoxy group at δ = 3.70 ppm. Secondary amine (*S*)-**297** was then treated with a second equivalent of 2-methoxybenzaldehyde, to yield the tertiary amine (*S*)-**298** in 98% yield (Scheme 155). The structure of amine (*S*)-**298** was identified by the absence of an aldehyde peak, with the resonances of the diastereotopic protons of the benzylic methylene group corresponding to four protons (δ = 3.45 and 3.69 ppm), and the methoxy group corresponding to six protons (δ = 3.68 ppm).

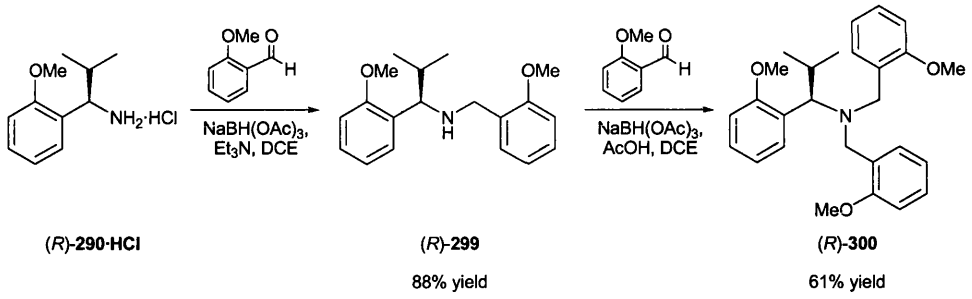



**Scheme 156** *Reductive amination of model system*

Due to the discovery that a small amount of the dialkylation product had been formed in the initial reductive amination step it was decided to attempt a one-pot 'double' reductive amination by treating α-methylbenzylamine with two equivalents of 2-methoxy benzaldehyde in the presence of sodium triacetoxyborohydride. However, this was found to be ineffective as a competing reaction involving the reduction of the aldehyde was found to predominate, meaning that the reaction did not proceed to completion, resulting in a mixture of products.

The efficient two-step synthesis of a tertiary amine containing protected phenolic groups was very promising and as a consequence these conditions were employed for the reductive amination of amine (*R*)-**290·HCl**. It was necessary to treat the amine

hydrochloride (*R*)-**290·HCl** with one equivalent of triethylamine to yield the free base, however this could be done *in situ*, followed by the addition of one equivalent of 2-methoxybenzaldehyde and 1.4 equivalents of sodium triacetoxyborohydride. This afforded secondary amine (*R*)-**299** in 88% yield after 24 hours (Scheme 157).




(*R*)-**290·HCl** (*R*)-**299** 88% yield (*R*)-**300** 61% yield

**Scheme 157** *Reductive amination of amine (R)-**290·HCl***

The product was identified by the presence of resonances corresponding to the benzylic methylene group at δ = 3.38 and 3.58 ppm and the absence of an aldehyde resonance. The resonances corresponding to the methyl groups were observed at δ = 0.68 and 0.87 ppm. A small amount of tertiary amine (*R*)-**300** was also observed. Secondary amine (*R*)-**299** was then further treated with 2-methoxybenzaldehyde and sodium triacetoxyborohydride to yield tertiary amine (*R*)-**300** as a pale yellow solid in 61% yield after recrystallisation from hexane. It was found that the addition of acetic acid, which acts as an acid catalyst, was necessary to improve the reaction rate. Tertiary amine (*R*)-**300** was identified by the absence of an aldehyde peak and the resonances corresponding to the benzylic methylene group (δ = 3.48 and 3.65 ppm) were now equivalent to four protons; the methoxy group adjacent to the *iso*-propyl unit was observed at δ = 2.92 ppm, whilst the other two were shown at δ = 3.03 ppm corresponding to six protons (Figure 107).

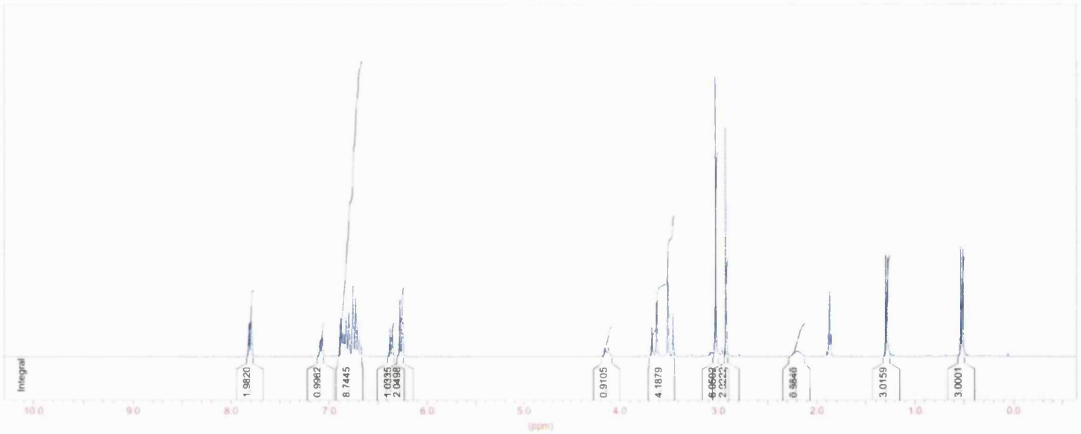


**Figure 107** *$^1$H NMR ($d_8$-toluene) spectrum of (R)-**300***

High resolution mass spectrometry identified the molecular mass of $[M+H]^+$ as 420.2537 ($C_{27}H_{34}NO_3$ requires 420.2533). In the low resolution spectrum there were signals at 256.2 corresponding to the molecular ion with the loss of the benzyl unit containing the *iso*-propyl group; 163.1 which is consistent with the mass of the benzyl unit containing the *iso*-propyl group; and 121.2 which correlates to the mass of the other benzyl unit. The structure of amine (*R*)-**300** was also confirmed by X-ray crystallography, which also confirmed the absolute configuration of amine **300** as the (*R*)-enantiomer (Figure 108).

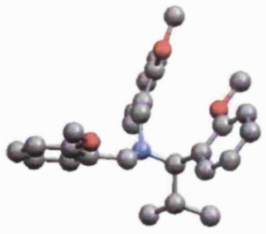
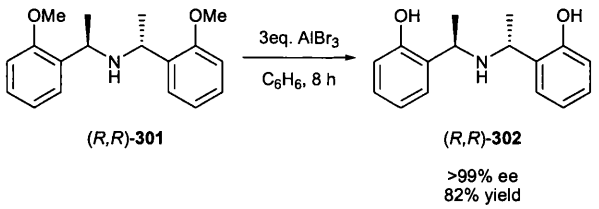


**Figure 108** *X-ray crystal structure of (R)-**300** (protons omitted for clarity)*

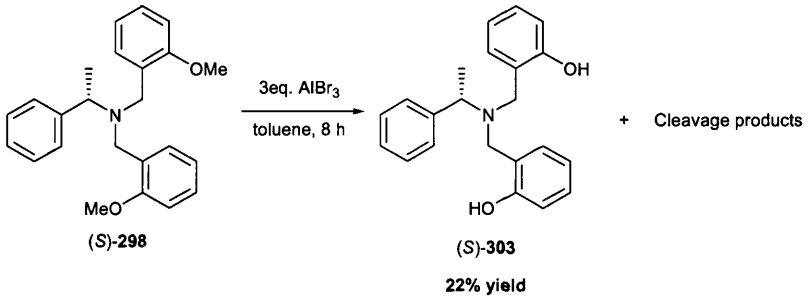
### 4.3.7 Cleavage of Methyl Aryl Ethers (*S*)-291 and (*R*)-300

In 2000, Kündig *et al.* reported the cleavage of methyl aryl ether (*R*,*R*)-**301** using aluminium tribromide in benzene, to afford amine (*R*,*R*)-**302** in 82% yield and >99% ee after eight hours (Scheme 158).[173] The authors noted that the use of boron tribromide or sodium ethanethiolate in this transformation resulted in competitive cleavage of the benzylic C-N bond.



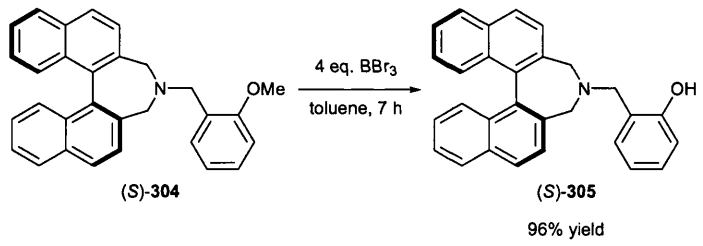

**Scheme 158** *Demethylation of amine (R,R)-**301** using aluminium bromide*

Thus, model system (*S*)-**298** was treated with three equivalents of aluminium tribromide in toluene for eight hours (Scheme 159). This resulted in a mixture of cleavage products and the demethylated product (*S*)-**303**, which was isolated in only 22% yield after precipitation with hexane. The low yield of this reaction meant that clearly another method of demethylation was required.




**Scheme 159** *Demethylation of model system (S)-**298** with aluminium bromide*

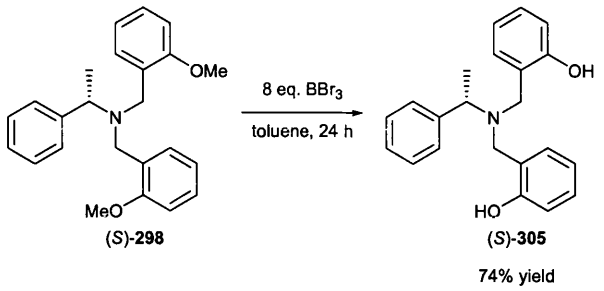
Despite the unsuccessful cleavage of (*R*,*R*)-**301** with boron tribromide reported by Kündig *et al.*,[173] the use of boron tribromide had been reported by Rosini *et al.* in the demethylation of methyl aryl ether (*S*)-**304**,[174] thus indicating how temperamental and reliant on the structure of the methyl phenyl ether, this type of methoxy deprotection reaction can be. Treatment of amine (*S*)-**304** with four equivalents of boron tribromide in toluene had resulted in amine (*S*)-**305** in 96% yield (Scheme 160).




**Scheme 160** *Demethylation of amine (S)-**304** with boron tribromide*

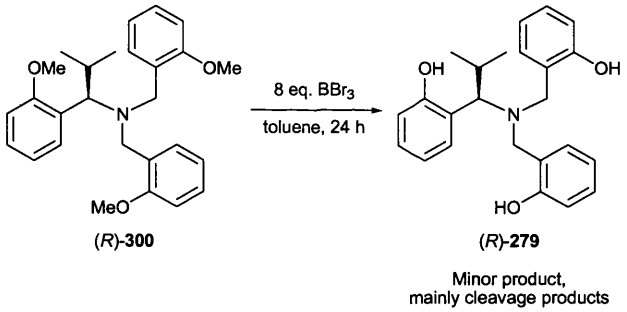
Thus, model amine (*S*)-**298** was treated with eight equivalents of boron tribromide in toluene. It was found that a reaction time of 24 hours was required for the reaction to

proceed to completion, resulting in deprotected amine (*S*)-**305** in 74% yield (Scheme 161). The product was identified by its $^1$H NMR spectrum, in which there was an absence of resonances relating to the methoxy groups and the presence of a broad singlet at $\delta$ = 5.10 ppm corresponding to the two hydroxyl protons.




**Scheme 161** *Demethylation of model amine (S)-**298** with boron tribromide*

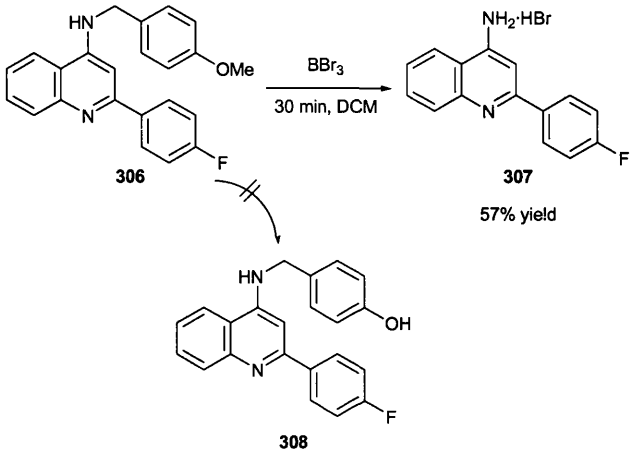
The subsequent treatment of (*R*)-**300** with twelve equivalents of boron tribromide resulted in a complete mixture of products without any trace of any (*R*)-**279** (Scheme 162). It was postulated that there was competitive cleavage of the benzylic C-N bond and so the reaction was repeated with only eight equivalents of boron tribromide. This again resulted in a mixture of cleavage products, and whilst (*R*)-**279** might have been present in very small amounts, it proved too elusive to be isolated *via* chromatographic purification.




**Scheme 162** *Attempted demethylation of amine (R)-**300** with boron tribromide*

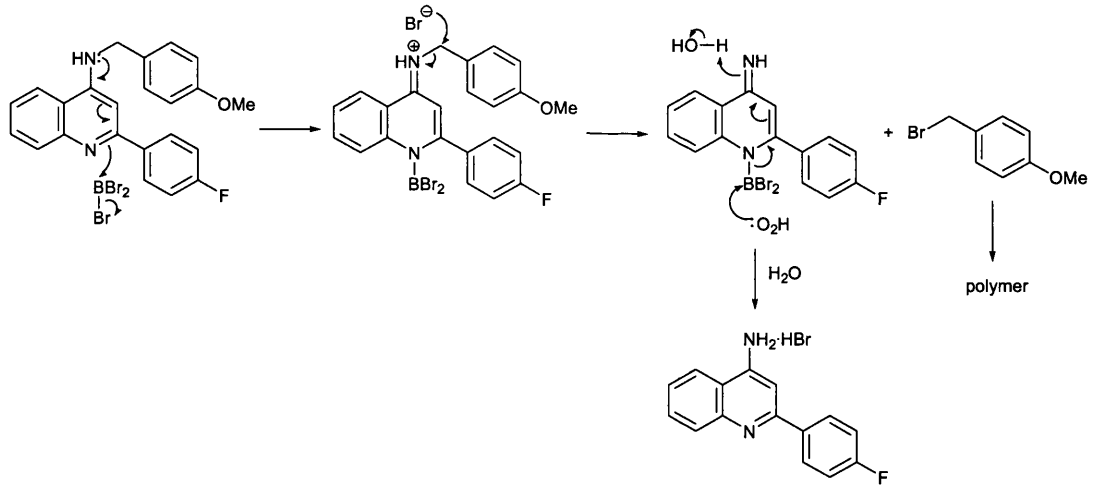
The reaction was then repeated with only three equivalents of boron tribromide and was monitored by $^1$H NMR spectroscopy. This revealed that the cleavage pathway of amine (*R*)-**300** appeared to predominate as after four hours, the $^1$H NMR spectrum showed significant amounts of cleavage products, but only traces of the partially deprotected product. After eight hours, the $^1$H NMR spectrum was seen to be a much more complex mixture of products. Whilst the difference in reactivity between amines (*S*)-**298** and (*R*)-**300** under these deprotection conditions was initially puzzling, a recent report by

Strekowski *et al.* indicated that competitive cleavage of the benzylic C-N was occurring.[175] In this report the authors attempted the demethylation of methyl phenyl ether **306** with boron tribromide, but whilst no demethylation product **308** was observed, primary amine **307** was found to be the major product (Scheme 163).




**Scheme 163** *Cleavage of benzyl amino groups by boron tribromide*

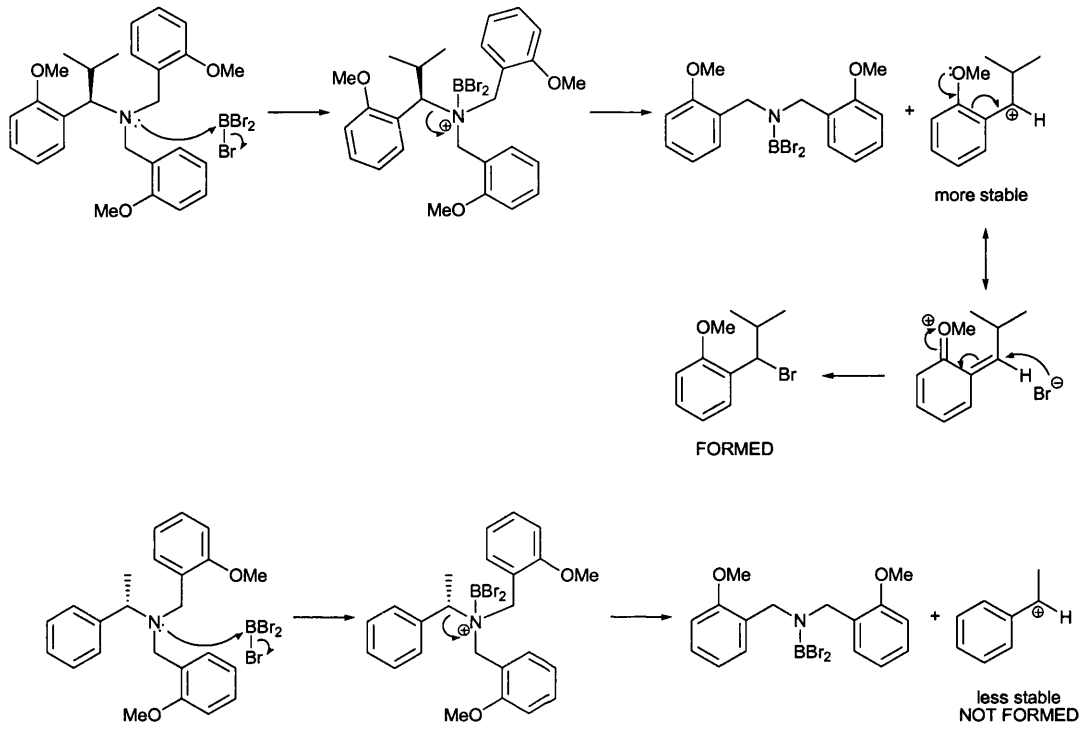
The mechanism for the debenzylation of **306** was believed to proceed *via* elimination of the benzyl group with bromide after coordination of the pyridine nitrogen to boron tribromide (Scheme 164).




**Scheme 164** *The mechanism of the debenzylation of amino benzyl groups*

Thus, it can be postulated that the mechanism of the cleavage of (*R*)-**300** proceeds *via* coordination of boron to the nitrogen atom followed by elimination of the substituted benzyl group. The subsequently formed carbocation is resonance stabilised by the lone pair of the methoxy group, which can then undergo attack by a bromide ion. This

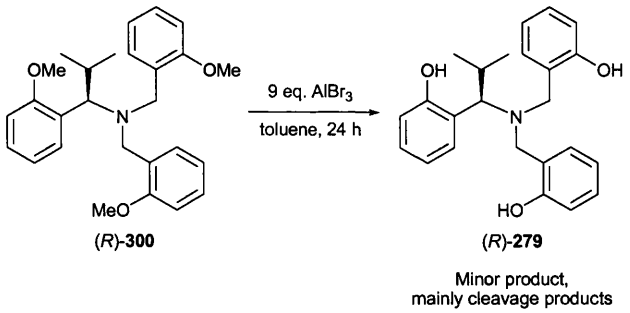
bromide product can then polymerise. A possible mechanism is shown in Scheme 165. When this mechanism is applied to amine (*S*)-**298** it is seen that the carbocation formed is much less stable. Thus, it is less likely to be formed, and cleavage of amine (*S*)-**298** is consequently less favourable than for amine (*R*)-**300**.




**Scheme 165** *Proposed mechanism for the cleavage of (R)-**300** and (S)-**298***

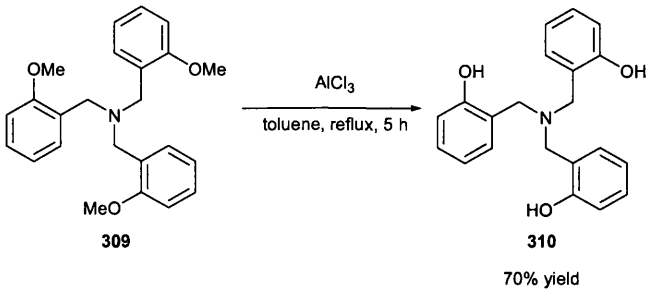
This mechanism is supported by the mass spectroscopy fragmentation of amine (*R*)-**300** in which there were signals at 256.2 corresponding to the molecular ion with the loss of the benzyl unit containing the *iso*-propyl group; 163.1 which is consistent with the mass of the benzyl unit containing the *iso*-propyl group and was the peak of the largest intensity (100%).

Methyl aryl ether (*R*)-**300** was also treated with aluminium tribromide, which unsurprisingly, resulted in a mixture of products, with deprotected (*R*)-**279** being present in small amounts (Scheme 166). Again, isolation proved difficult.



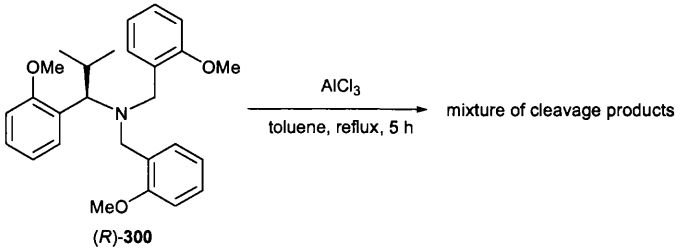

**Scheme 166** *Attempted demethylation of methyl aryl ether (R)-**300** with aluminium tribromide*

The demethylation of methyl aryl ether **309** using aluminium trichloride has been reported by Koch *et al.*[124] In this procedure, amine **309** was refluxed with five equivalents of aluminium chloride in toluene for five hours to afford amine **310** in 70% yield (Scheme 167).




**Scheme 167** *Demethylation of methyl aryl ether **309** with aluminium trichloride*

Consequently, methyl aryl ether (*R*)-**300** was refluxed with five equivalents of aluminium chloride (Scheme 168). The reaction was monitored by thin layer chromatography and the starting material was found to be consumed after five and a half hours. Analysis of the crude material by $^1$H NMR revealed that the product did not appear to be present. It was therefore clear that an alternative demethylation strategy was necessary.



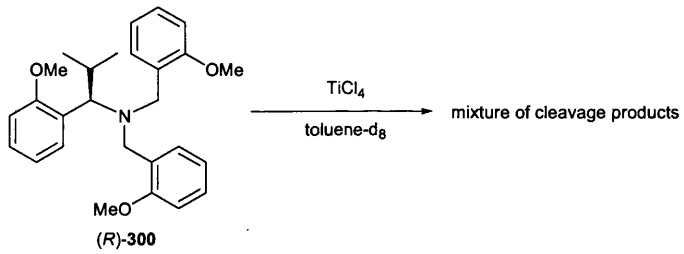

**Scheme 168** *Attempted demethylation of methyl aryl ether (R)-**300** using aluminium trichloride*

### 4.3.8 Other Demethylation Strategies

In despair, a range of other demethylation strategies which have been shown to efficiently cleave aryl methyl ethers were also attempted. It was decided to use methyl aryl ether (*R*)-**300** as a substrate because the strategy of using amine (*S*)-**298** as a model compound for deprotection studies had been shown to be unsuccessful.

#### Titanium(IV) Chloride

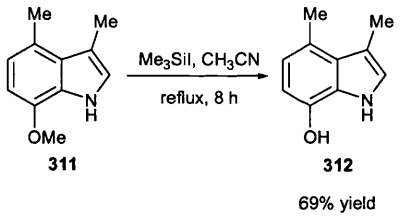
It was decided to attempt the demethylation of amine (*R*)-**300** with titanium(IV) chloride as the Lewis acid (Scheme 169). The first reaction attempted used five equivalents of titanium(IV) chloride in deuterated toluene. Unfortunately, this resulted in an indiscernible mixture of cleavage products. Using only one equivalent of titanium(IV) chloride did not improve the result. It was found that the use of titanium(IV) *iso*-propoxide resulted in the recovery of the starting material.




**Scheme 169** *Attempted demethylation of (R)-**300** using titanium(IV) chloride*

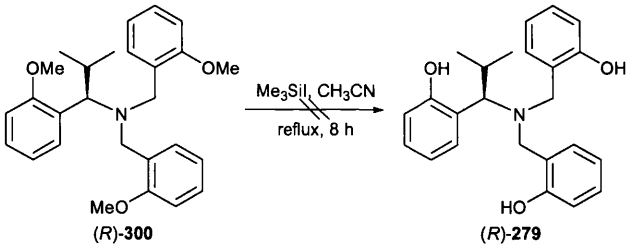
#### Trimethylsilyl iodide in Acetonitrile[176]

This procedure was published by Fukuzumi *et al.* in 1997 to cleave aryl methyl ether **311**, resulting in 3,4-dimethyl-1H-indol-7-ol **312** in 69% yield (Scheme 170).[176]




**Scheme 170** *Demethylation of **311** using trimethylsilyl iodide*

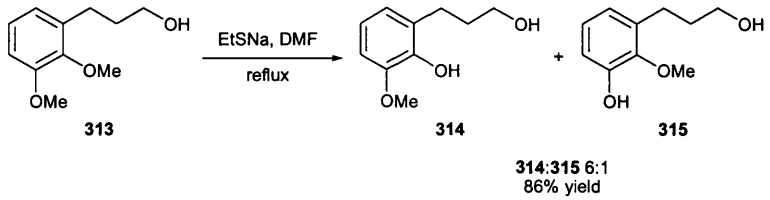
Application of this procedure to amine (*R*)-**300**, resulted in no reaction after 24 hours (Scheme 171); however, the 'silver lining' was the recovery of starting material that could be reused!




**Scheme 171** *Attempted demethylation of (R)-**300** using trimethylsilyl iodide*

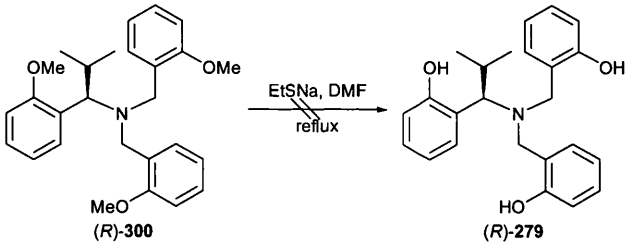
### Treatment with Sodium Ethanethiolate in refluxing DMF[177,178]

In 1987, Salomon *et al.* reported the demethylation of **313** using sodium ethanethiolate, formed *in situ* from sodium hydride and ethanethiol, in refluxing DMF.[177] This resulted in a mixture of mono-methoxy phenols **314** and **315** in a 6:1 ratio and 86% yield (Scheme 172).




**Scheme 172** *Demethylation of **313** with sodium ethanethiolate*

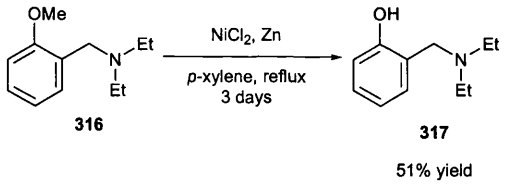
Treatment of methyl aryl ether (*R*)-**300** with three equivalents of sodium ethanethiolate, formed *in situ*, resulted in mainly starting material, with some by-products, but the demethylated product (*R*)-**279** was not observed (Scheme 173).




**Scheme 173** *Attempted demethylation of amine (R)-**300** using sodium ethanethiolate*

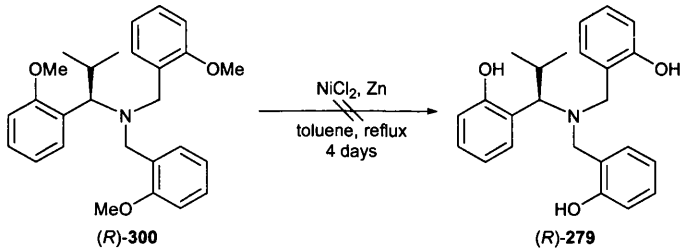
### Nickel Chloride and Zinc[178]

In 2001, Yonezawa *et al.* reported the use of nickel chloride and zinc to cleave aryl alkyl ethers.[179] For example, treatment of phenyl methyl ether **316** with nickel chloride and zinc in xylene resulted in amine **317** in 51% yield (Scheme 174).




**Scheme 174** *Demethylation of phenyl methyl ether* ***309*** *with nickel chloride and zinc*

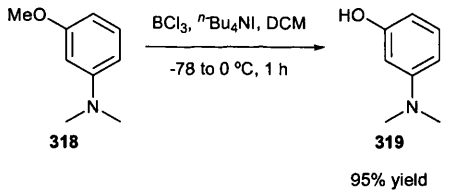
Subsequent treatment of (*R*)-**300** under these conditions in toluene for 4 days resulted in no reaction and only the starting material was recovered (Scheme 175).




**Scheme 175** *Attempted demethylation of amine (R)-****300*** *with nickel chloride and zinc*

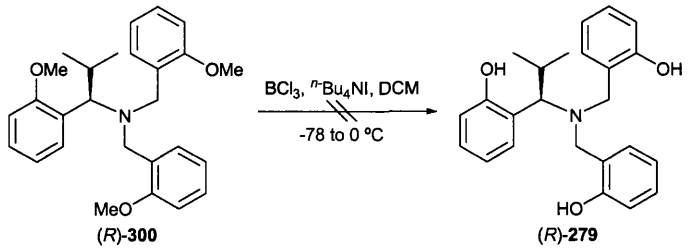
### Boron Trichloride and Tetra-$^{n}$Butylammonium iodide[180]

In 1999, Coe *et al.* reported the use of a combination of boron trichloride and tetra-$^{n}$-butylammonium iodide for the efficient demethylation of a range of phenyl methyl ethers.[180] A representative example is shown in Scheme 176, in which 3-(dimethylamino) phenol **319** was obtained in 95% yield after 1 hour at 0 °C.




**Scheme 176** *Demethylation of* ***318*** *with boron trichloride and tetra-$^{n}$butylammonium iodide*

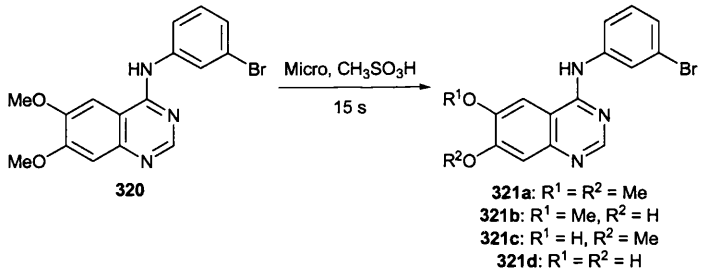
Treatment of methyl aryl ether (*R*)-**300** with boron trichloride and tetra-$^{n}$butyl ammonium iodide resulted in consumption of the starting material after 90 minutes (Scheme 177). Analysis of the $^{1}$H NMR spectrum confirmed that the starting material had been consumed, but no demethylated product appeared to be present. Instead, resonances consistent with the possible formation of a boron complex with (*R*)-**300** were observed. Peaks corresponding to the non-equivalent methoxy groups were observed at $\delta$ = 3.72 and 3.89 ppm, which are shifted downfield from the peaks observed for the starting material.




**Scheme 177** *Attempted demethylation of amine (R)-**300** with boron trichloride and tetra-$^{n}$butylammonium iodide*

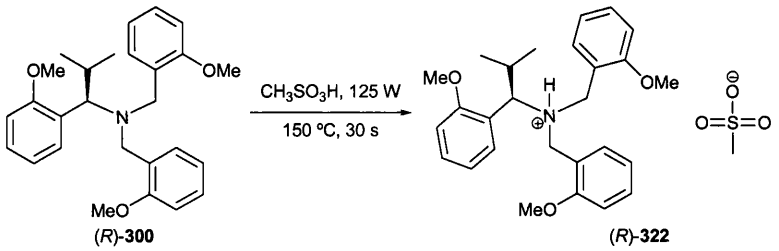
### Microwave with Methanesulphonic Acid[181]

In 2002, Fredriksson *et al.* reported the demethylation of amine **320** *via* treatment with methanesulphonic acid in a microwave (Scheme 178).[181] This resulted in a mixture of demethylated products **321a-d** in varying ratios dependant on the wavelength used. An unidentified side product was also obtained.




**Scheme 178** *Demethylation of **320** with methanesulphonic acid in a microwave*

Nevertheless, methyl aryl ether (*R*)-**300** was treated in a microwave with methanesulphonic acid for 30s at 125W and 150 °C (Scheme 179). This resulted in a dark red solution which when washed with ethyl acetate afforded the protonated ligand salt (*R*)-**322**, which was identified by the following resonances in its $^{1}$H NMR spectrum: $\delta$ = 3.68 and 3.80 ppm corresponding to the two methoxy groups; $\delta$ = 4.80 ppm representing the methine proton adjacent to the nitrogen; and $\delta$ = 4.59 ppm corresponding to the ammonium proton. The methyl group of the methanesulphonate was observed at $\delta$ = 2.83 ppm.

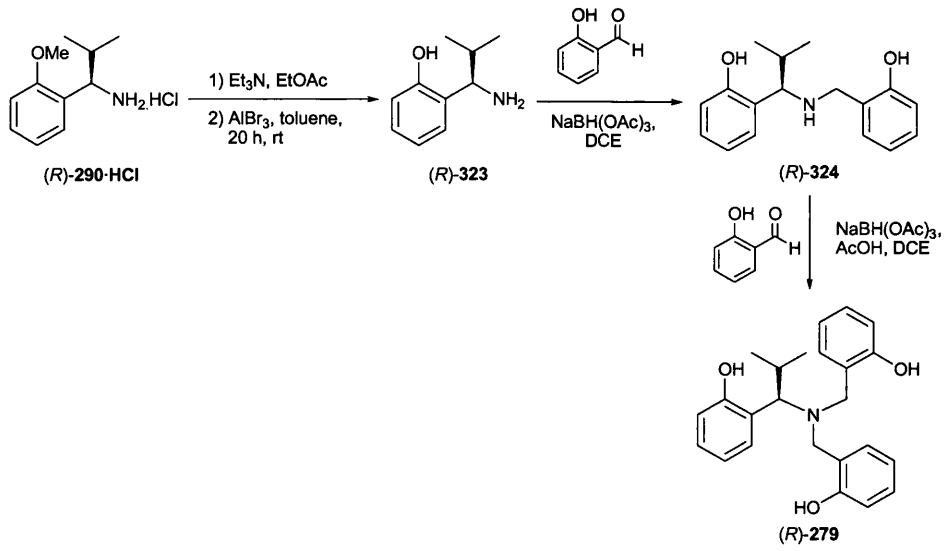



**Scheme 179** *Attempted demethylation of (R)-**300** with methanesulphonic acid in a microwave*

This result is interesting in itself as it demonstrates that the lone pair of the central nitrogen atom is sterically accessible for reaction. Neutralisation of the reaction mixture with 1 M sodium hydroxide resulted in the recovery of ligand (*R*)-**300** with small amounts of cleavage products.

## 4.4 Alternative Synthesis of (*R*)-279

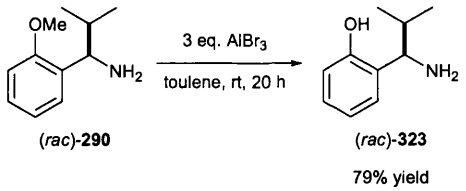
It became clear that an alternative synthesis of (*R*)-**279** was necessary, which did not involve demethylation of tris(aryl methyl ether) (*R*)-**300**. Our first strategy was to cleave the aryl methyl ether of the primary amine (*R*)-**290·HCl** and then perform a double reductive amination on this amine using 2-hydroxybenzaldehyde to yield (*R*)-**279** (Scheme 180). It was reasoned that whilst the methoxy protecting group was necessary for the asymmetric synthesis of amine (*R*)-**290·HCl**, it may not be necessary for the subsequent reductive aminations.




(*R*)-**290·HCl** (*R*)-**323** (*R*)-**324** (*R*)-**279**

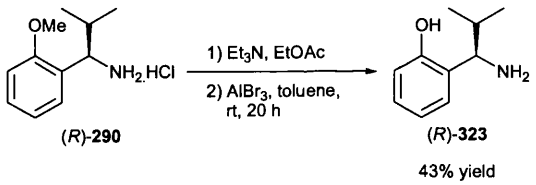
**Scheme 180** *Proposed alternative synthesis of (R)-**279***

The demethylation of (*rac*)-**290** has been reported by Kündig *et al.*[168] This involved the treatment of (*rac*)-**290** with three equivalents of aluminium tribromide at room temperature for twenty hours (Scheme 181). This resulted in 2-(1-amino-2-methyl propyl)phenol (*rac*)-**323** in 79% yield.



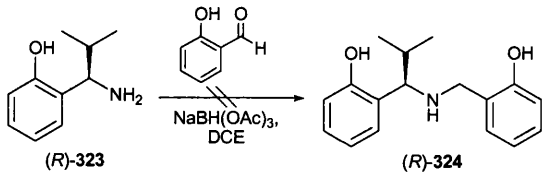

**Scheme 181** *Demethylation of (rac)-**290** with aluminium tribromide*

Thus, (*R*)-**290·HCl** was treated with triethylamine in ethyl acetate to yield the free base (*R*)-**290** in quantitative yield, followed by the treatment with aluminium tribromide in toluene (Scheme 182). This resulted in (*R*)-2-(1-amino-2-methylpropyl)phenol **323** in a poor yield (43%). The product was confirmed by analysis of the $^{1}$H NMR spectrum, which revealed an absence of a resonance at $\delta$ = 3.73 ppm corresponding to the loss of the methyl group. This was also confirmed in the $^{13}$C NMR spectrum with the absence of a peak at $\delta$ = 55.7 ppm.




**Scheme 182** *Demethylation of (R)-**290** with aluminium tribromide*

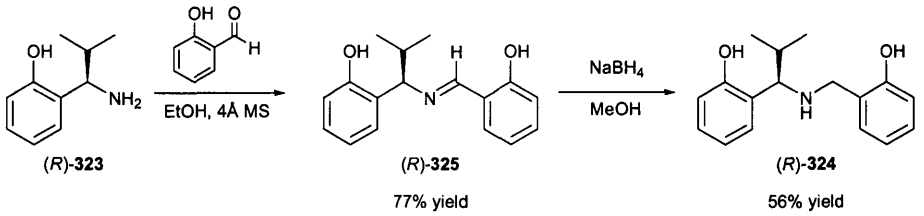
Subsequent reaction of amine (*R*)-**323** with 2-hydroxybenzaldehyde and sodium triacetoxyborohydride in DCE, unfortunately resulted in a complex mixture of products, with no secondary amine observed (Scheme 183).




**Scheme 183** *Attempted reductive amination of amine (R)-**323***

It was thus decided to form secondary amine (*R*)-**323** *via* a two-step strategy involving the formation of imine (*R*)-**325** followed by its reduction (Scheme 184). Formation of (*R*)-*N*-(2-hydroxybenzylidene)-1-(2-methoxyphenyl)-2-methylpropan-1-amine (*R*)-**325** from amine (*R*)-**323** and 2-hydroxybenzaldehyde in ethanol resulted in (*R*)-**325** in 77% yield as a yellow powder. Its structure was identified *via* $^{1}$H NMR spectroscopy which confirmed the presence of an imine with a chemical shift at $\delta$ = 8.67 ppm. Subsequent reduction of this imine with sodium borohydride resulted in amine (*R*)-**324** in only 56%

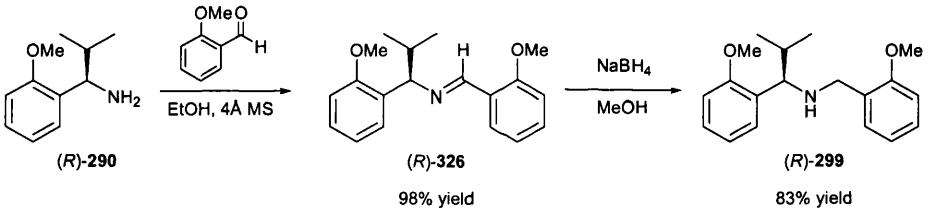
yield. Spectroscopic analysis revealed the absence of a resonance relating to the imine and the presence of an AB quartet at $\delta$ = 3.51 and 3.83 ppm ($J$ = 13.2 Hz) corresponding to the benzylic methylene group.




(*R*)-**323** (*R*)-**325** 77% yield (*R*)-**324** 56% yield

**Scheme 184** *Stepwise formation of secondary amine (R)-**324***

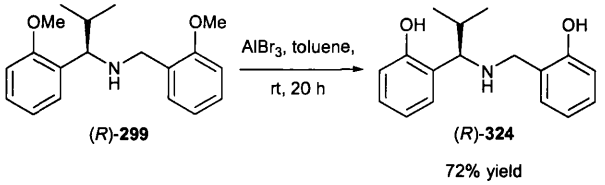
The low yield of the demethylation of amine (*R*)-**290** together with the low yield of the last step of the above synthesis are not ideal and so another synthesis of (*R*)-**324** was attempted, involving the formation of the secondary amine (*R*)-**299** followed by demethylation. Amine (*R*)-**299** was formed *via* the stepwise formation of an imine followed by its reduction, in order to circumvent dialkylation which occurs during the one-pot reductive amination (Scheme 185). This resulted in amine (*R*)-**299** in 83% yield from the imine.




(*R*)-**290** (*R*)-**326** 98% yield (*R*)-**299** 83% yield

**Scheme 185** *Stepwise formation of amine (R)-**299***

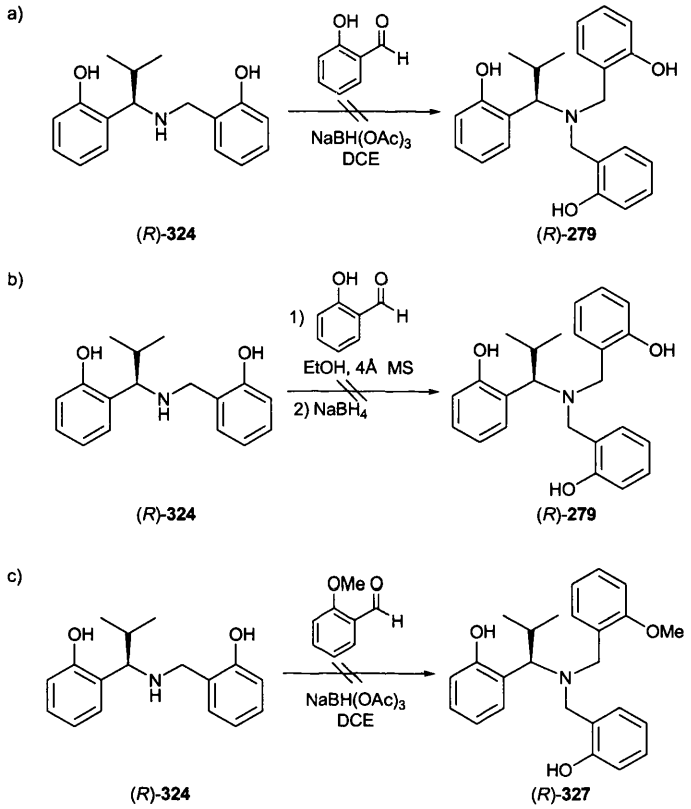
Unabashed by previous poor results for demethylation of phenyl methyl ethers, the deprotection of the secondary amine (*R*)-**299** with aluminium tribromide was attempted (Scheme 186). This fortuitously resulted in amine (*R*)-**324** in 72% yield as a brown oil. The $^{1}$H NMR confirmed the absence of the methoxy groups. This was also visible in the $^{13}$C NMR spectrum.




(*R*)-**299** (*R*)-**324** 72% yield

**Scheme 186** *Alternative synthesis of secondary amine (R)-**324***

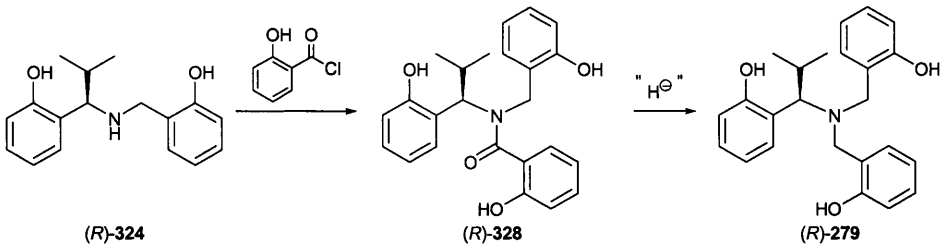
Buoyed by the success of this reaction, which afforded amine (*R*)-**324** in a higher overall yield than the previous synthesis, both the one-pot and stepwise reductive amination with 2-hydroxybenzaldehyde was attempted (Scheme 187a, b). Unfortunately, these reactions were both found to be unsuccessful, with an undecipherable mixture of products being observed in $^1$H NMR spectra in both cases. The reductive amination of amine (*R*)-**324** with 2-methoxybenzaldehyde was also attempted (Scheme 187c). This also resulted in a mixture of products.




**Scheme 187** *Attempted reductive aminations of (R)-**324***

## 4.5 Synthesis of (*R*)-279 *via* Amide Synthesis

Undaunted, it was decided to attempt an alternative synthesis of amine (*R*)-**279** involving the formation and subsequent reduction of an amide (Scheme 188). 2-Hydroxybenzoyl chloride was not commercially available and so it was clear that a coupling reagent was necessary to mediate this reaction.




**Scheme 188** *Proposed synthesis of (R)-**279** via amide (R)-**328***

### 4.5.1 Amide Formation using a Coupling Agent

In 1999 Hayes reported the use of the combination of 1,3-dicyclohexylcarbodiimide (DCC) **329** and 1-hydroxybenzotriazole (HOBt) **330** (Figure 109) to couple 2-((methylamino)methyl)phenol **331** and *N*-Z-L-aspartic acid-β-methyl ester (*S*)-**332** affording amide (*S*)-**333** in 81% yield (Scheme 189).[182]

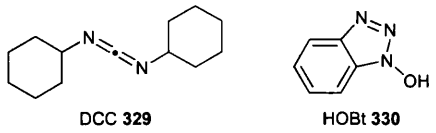
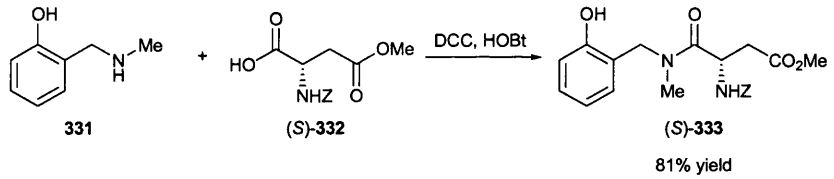



**Figure 109** *1,3-Dicyclohexylcarbodiimide (DCC) **329** and 1-hydroxybenzotriazole (HOBt) **330***




**Scheme 189** *Amide coupling mediated by DCC*

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (EDC) **334** (Figure 110) has also been demonstrated as a coupling agent for related reactions. For example, the coupling of amine **335** and phenylpropiolic acid **336** afforded amide **337** in 62% yield (Scheme 190).[183]

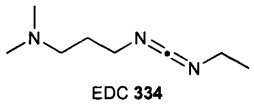
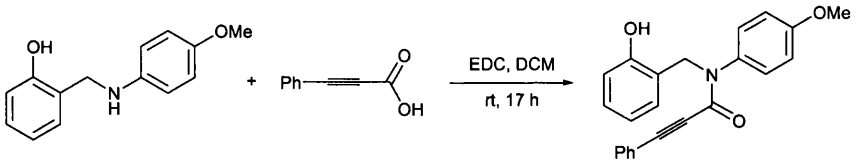



**Figure 110** *1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (EDC) **334***



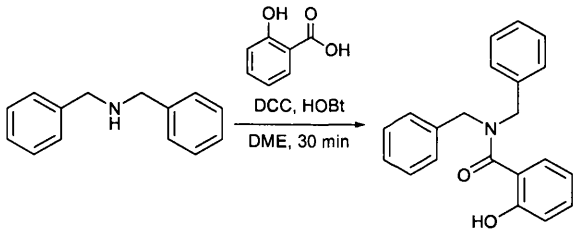

335 336 337

62% yield

**Scheme 190** *Amide coupling mediated by EDC*

### Formation of *N,N*-Dibenzyl-2-Hydroxybenzamide 339

Despite the ineffectualness of using a model system in the case of attempting to find a demethylation strategy, it was decided to use a model system to find the optimal amide formation conditions. Thus, dibenzylamine **338** was chosen as a suitable model for amine (*R*)-**324** and was consequently treated with 2-hydroxybenzoic acid, DCC, and HOBt in DME (Scheme 191). The reaction was monitored by TLC and was deemed to be complete after 30 minutes. Column chromatography afforded *N,N*-dibenzyl-2-hydroxybenzamide **339** in 43% yield. The formation of the product was confirmed by the presence of a chemical shift in the $^{1}$H NMR corresponding to the benzylic protons at $\delta$ = 4.61 ppm which had shifted downfield from the analogous peak for the starting material ($\delta$ = 3.75 ppm). The structure of the amide was also evidenced by a resonance in the $^{13}$C NMR spectrum at $\delta$ = 172.9 ppm corresponding to the amide carbonyl.

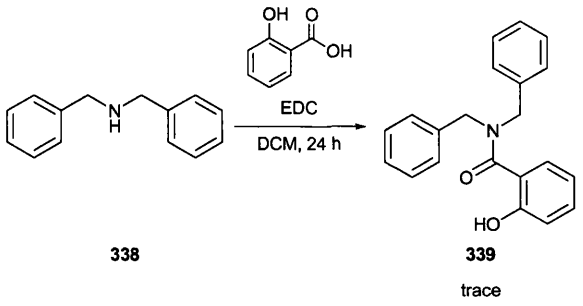



338 339

43% yield

**Scheme 191** *DCC coupling of dibenzylamine **338** and 2-hydroxybenzoic acid*

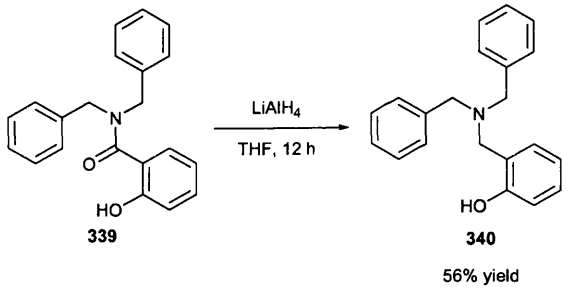
An amide coupling using EDC was attempted due to the poor yield of the previous coupling (Scheme 192); however, this reaction proved to be very slow, with a negligible amount of product being formed after 24 hours.




**Scheme 192** *EDC coupling of dibenzylamine **338** and 2-hydroxybenzoic acid*

### 4.5.2 Formation of 2-[(Dibenzylamino)methyl]phenol 340

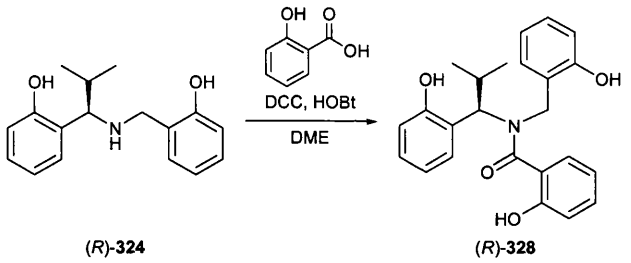
Amide **339** was then reduced with lithium aluminium hydride to form 2-((dibenzylamino)methyl)phenol **340** in 56% yield (Scheme 193). The structure of the product was confirmed by the $^1$H NMR which revealed the presence of a chemical shift at $\delta$ = 3.64 ppm corresponding to the newly formed benzylic group. The other benzylic protons were seen at $\delta$ = 3.52 ppm which is shifted when compared to amide **339**.




**Scheme 193** *Reduction of amide **339** with lithium aluminium hydride*

### 4.5.3 Amide Formation using Amine (*R*)-324

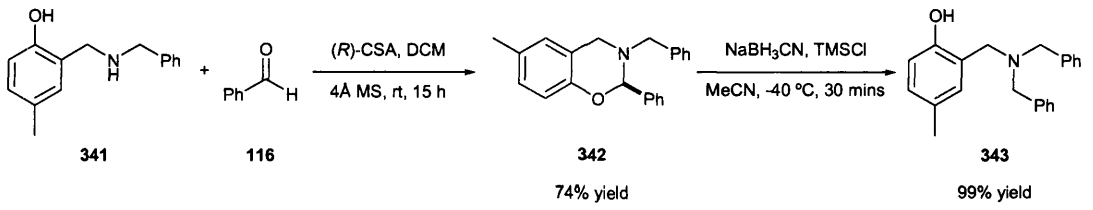
Although this synthesis had only proceeded to a 24% overall yield due to the low yield of the amide formation step, it was decided to attempt the amide synthesis with amine (*R*)-**324**. Thus, amine (*R*)-**324** was treated with 2-hydroxybenzoic acid, DCC, and HOBt (Scheme 194). Unfortunately, the reaction resulted in a complex mixture of products which in comparison to the crude reaction product of **338** (Scheme 192), did not appear to include the desired amide.




**Scheme 194** *Attempted amide coupling of (R)-**324** and 2-hydroxybenzoic acid with DCC*

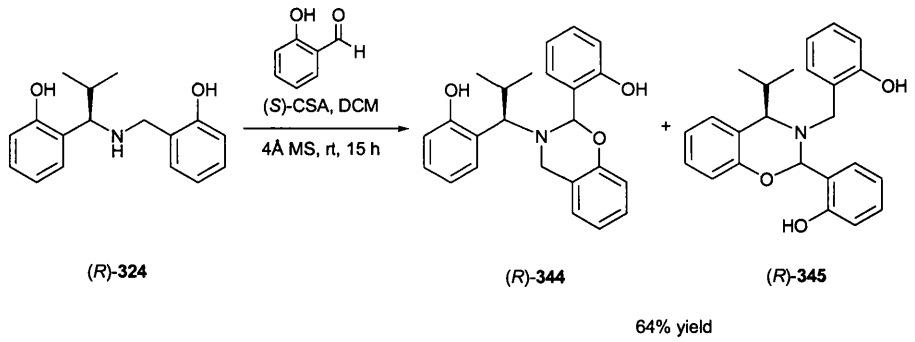
## 4.6 Synthesis of (*R*)-279 *via* a Cyclic Aminol Ether

In 2000, Bulman Page *et al.* reported the formation and consequent reductive cleavage of cyclic aminol ethers.[184] A representative example is the reaction of 2-((benzylamino) methyl)-4-methylphenol **341** with benzaldehyde **116** and (*R*)-(-)-10-camphorsulphonic acid ((*R*)-CSA) in DCM to yield cyclic aminol ether **342** in 74% yield (Scheme 195). This was then cleaved *via* a modified Eschweiler-Clarke procedure, using sodium cyanoborohydride as the hydride source, to yield 2-((dibenzylamino)methyl)-4-methylphenol **343** in 99% yield.




**Scheme 195** *Formation and subsequent cleavage of cyclic aminol ether **342** to yield tertiary amine **343***

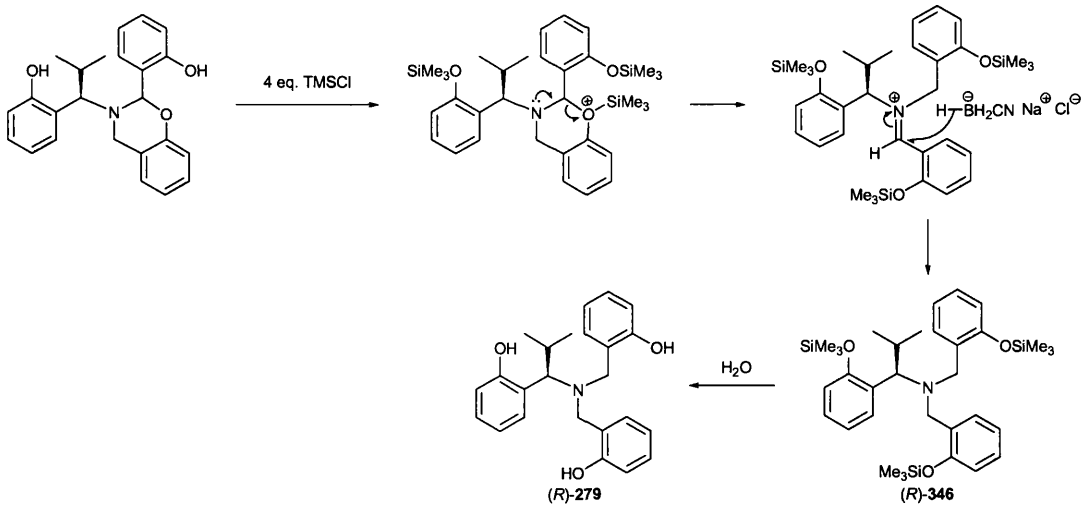
Thus, amine (*R*)-**324** was treated with 2-hydroxybenzaldehyde and (*S*)-CSA in DCM (Scheme 196). As expected the $^1$H NMR revealed a mixture of cyclic aminol ethers **344** and **345** in a 64% yield. The structures of the two products were confirmed by spectroscopic analysis which revealed a complex, broad spectrum corresponding to the formation of the two cyclic aminol ethers.




**Scheme 196** *Formation of cyclic aminol ethers (R)-**344** and (R)-**345***

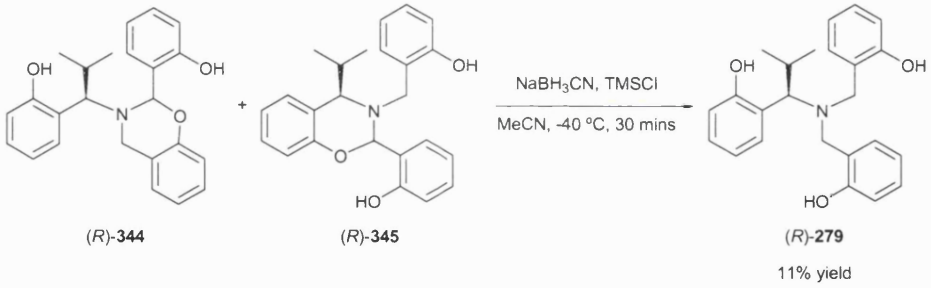
The two aminol ether products were not isolated individually and the mixture was subsequently cleaved reductively under the modified Eschweiler-Clarke procedure reported by Bulman Page *et al.*[184] In total four equivalents of chlorotrimethylsilane were required: one to mediate the reductive cleavage, two to account for the two free hydroxyl groups in the starting material as well as one to compensate for the competing reduction of chlorotrimethylsilane by sodium cyanoborohydride.

The reductive cleavage of cyclic aminol ethers (*R*)-**344** and (*R*)-**345** is believed to proceed *via* an iminium ion; a representative example is shown in Scheme 197. Chlorotrimethylsilane coordinated to the oxygen of the aminol ether and subsequent elimination by the lone pair of nitrogen resulted in an iminium ion. Reduction of this afforded the trimethylsilyl protected tris-phenol (*R*)-**346**, that is silyl deprotected on aqueous work up to yield (*R*)-**279**.




**Scheme 197** *Proposed mechanism for the reductive cleavage of cyclic aminol ethers*

Thus, treatment of cyclic aminol ethers (*R*)-**344** and (*R*)-**345** with chlorotrimethylsilane by sodium cyanoborohydride afforded a mixture of products (Scheme 198). This crude mixture was partially purified *via* the addition of hexane which precipitated many of the impurities to afford the desired product (*R*)-**279**, which was identified *via* $^1$H NMR analysis, which revealed two doublets at $\delta$ = 0.71 and 0.92 ppm and a multiplet at $\delta$ = 1.90-2.01 ppm corresponding to the two methyls and the proton of the *iso*-propyl unit respectively; and a double was observed at = 3.34 ppm, corresponding to the proton adjacent to the nitrogen and two doublets were observed at $\delta$ = 3.49 and 3.81 ppm representing the four diastereotopic benzylic protons (Figure 111). This was compared to the $^1$H NMR of amine (*R*)-**324** which, as expected, had a similar $^1$H NMR spectrum, thus implying that some (*R*)-**279** had been formed (Figure 112). The reaction was performed on a small scale and the product was obtained in only an 11% yield. Further purification *via* small scale column chromatography was attempted, but unfortunately the product was not recovered, and so further analysis was not possible. Due to time constraints and the need re-synthesise amine (*R*)-**324** this reaction could not be repeated.




**Scheme 198** *Reductive cleavage of cyclic aminol ethers (R)-**344** and (R)-**345** to yield amine (R)-**279***

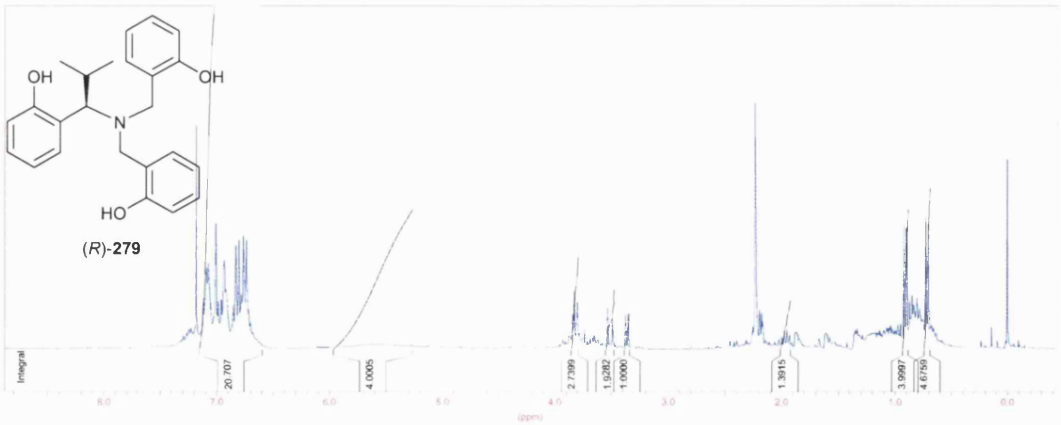



**Figure 111** *$^1$H NMR spectrum of partially purified (R)-**279***

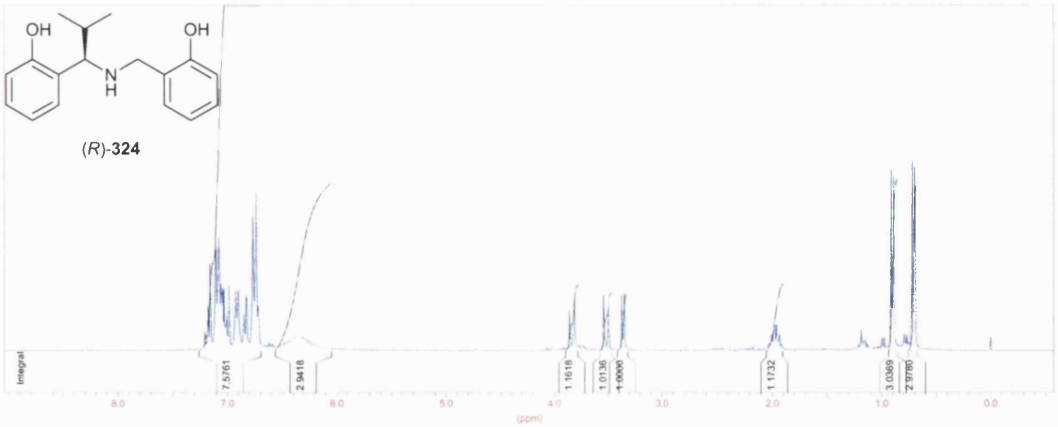
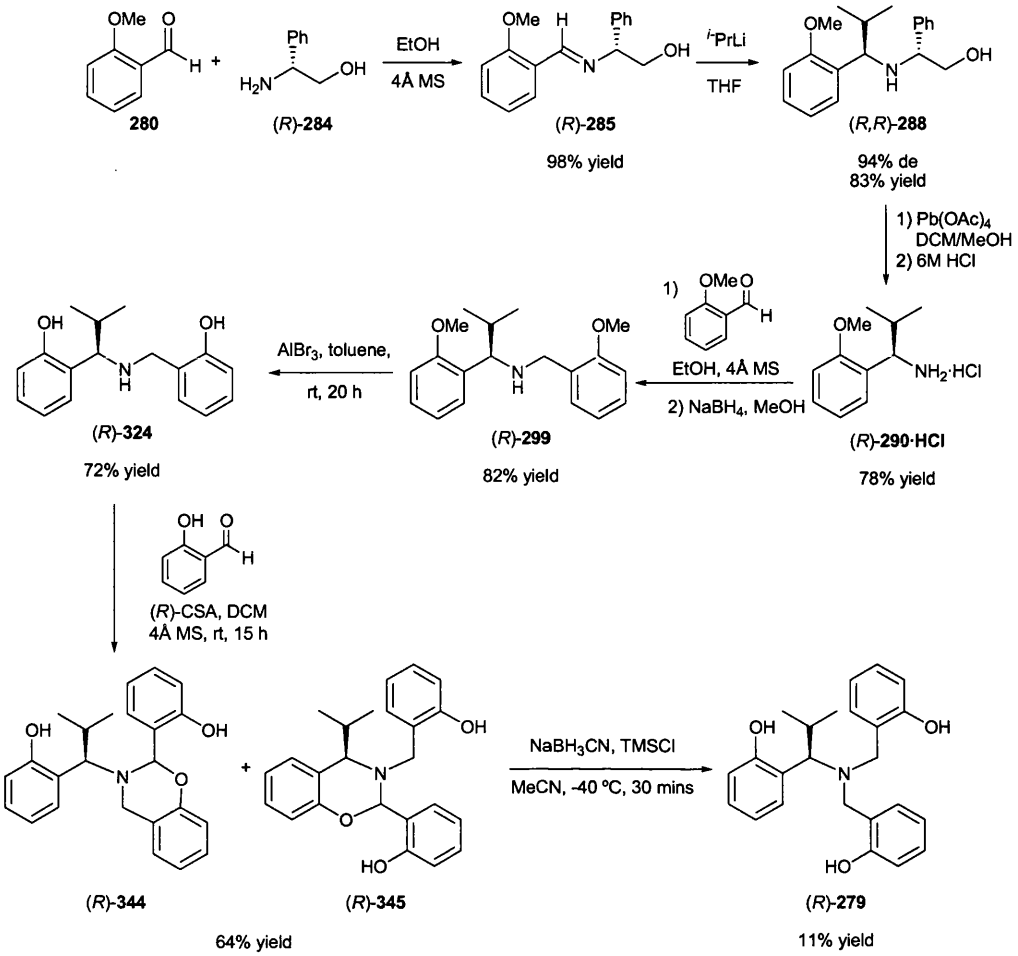



**Figure 112** *$^1$H NMR spectrum of amine (R)-**324** for reference*

## 4.7 Conclusion

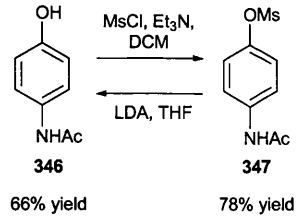
Chiral ligand (*R*)-**279** was eventually synthesised in a small amount *via* the protocol described in Scheme 199. Therefore, asymmetric addition to imine (*R*,*R*)-**285**, followed by deprotection of amine (*R*,*R*)-**288** with lead(IV) acetate. A stepwise reductive amination of the resulting primary amine (*R*)-**290** and cleavage of the phenol methyl ethers afforded amine (*R*)-**324** in 46% yield from amine (*R*,*R*)-**288**. This was treated with 2-hydroxybenzaldehyde to afford cyclic aminol ethers (*R*)-**344** and (*R*)-**345** which were cleaved *via* treatment with chlorotrimethylsilane, to yield ligand (*R*)-**279** in 3% overall yield. Whilst this synthesis of ligand (*R*)-**279** is clearly inefficient in its current state, it appears to have provided a route to the desired amine. Consequently, another member of the SDB group is now looking to optimise this route to provide sufficient quantities of (*R*)-**279** to enable chiral titanium complexes such as (*R*)-**347** to be prepared (Section 4.8, Scheme 202).




**Scheme 199** *Overall synthesis of ligand (R)-**279***

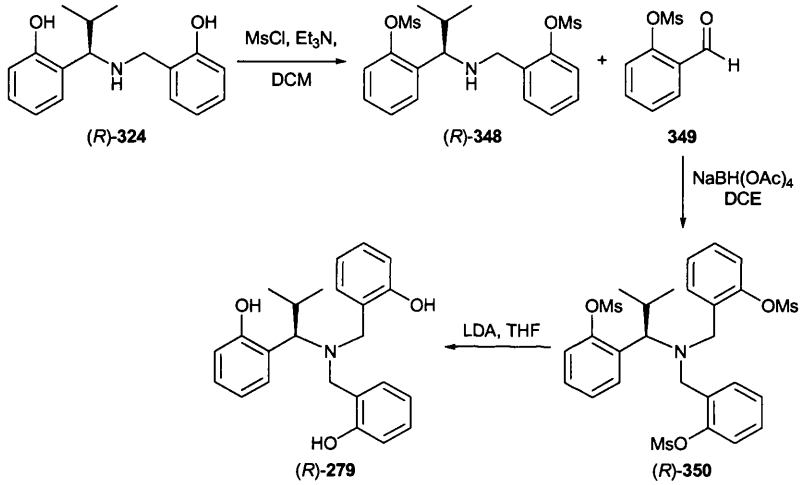
## 4.8 Future Work

The obvious next step in this project is the optimisation of the synthetic route to (*R*)-**279**. Another possible strategy is the use of more labile protecting groups on the phenolic groups. A recent publication by Carreira *et al.* described the mild cleavage of methane sulphonate as a protecting group for a range of phenols.[185] For example, 4-acetamidophenol **346** was protected using mesyl chloride, resulting in methanesulphonic acid 4-acetamido-phenyl ester **347** in 78% yield. The deprotection of this mesylate was demonstrated by the use of LDA, affording amidophenol **346** in 66% yield (Scheme 200).



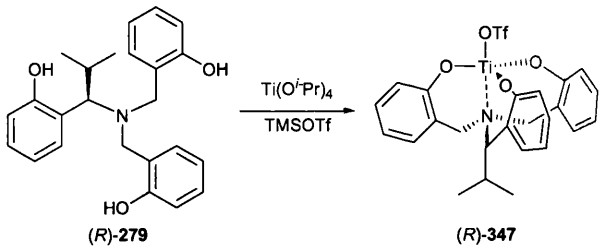

**Scheme 200** *Application of the methane sulphonate protecting group*

Thus, it is proposed that the mesylate of amine (*R*)-**324** could be employed in a reductive amination reaction with 2-formylphenyl methanesulfonate **349**, both of which are envisaged to be formed under the conditions described above, to form the mesyl protected triphenol (*R*)-**350** (Scheme 201). Subsequent deprotection using LDA would yield (*R*)-**279**.




**Scheme 201** *Proposed alternative synthetic rout for (R)-**279***

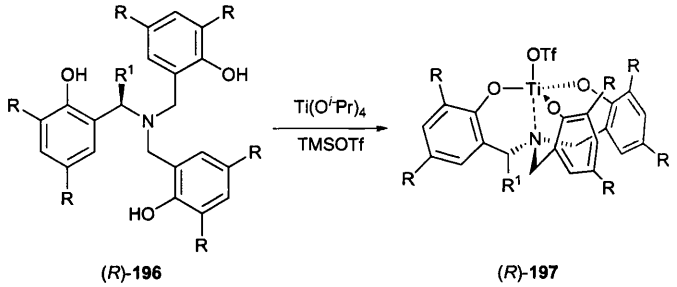
Other protecting groups which could be considered include methoxymethyl (MOM), benzyl (Bn), and bulky silyl groups such as tri-*iso*-propylsilyl (TIPS). After the synthetic route for (*R*)-**279** has been optimised, the next step would be the formation of the titanium complex of (*R*)-**279**, *via* treatment with titanium(IV) *iso*-propoxide and trimethylsilyl triflate (Scheme 202) and its screening in a range of asymmetric transformations, including the *aza*-Diels Alder, the diethyl zinc addition to benzaldehyde, the allyltributyltin addition to benzaldehyde, and the conventional Diels Alder.




(*R*)-**279** (*R*)-**347**

**Scheme 202** *Formation of pseudo-$C_3$-symmetric complex (R)-**347***

A family of novel ligands based on ligand (*R*)-**196** can then be synthesised following this procedure; of special interest are those ligands where R = Me, and $^t$Bu, which when complexed to a metal will further induce a chiral coordination sphere around the metal centre (Scheme 203).




(*R*)-**196** (*R*)-**197**

**Scheme 203** *Ligand (R)-**196** and its titanium complex*

# CHAPTER 5:
# *Experimental*

# 5 EXPERIMENTAL

## 5.1 General Procedures

Infra red spectra (4000 to 600cm$^{-1}$) were recorded from thin films or $CDCl_3$ solutions on a Perkin Elmer (1600) FT spectrometer with internal calibration. Only selected absorbances are quoted as ν in cm$^{-1}$, and designated st, strong; m, medium; w, weak; br, broad.

All capillary melting points were measured using a Büchi 535 melting point apparatus. The readings were taken from a mercury-in-glass thermometer and are reported uncorrected as the meniscus point, rounded to the nearest 1 °C with a heating ramp rate of 0.5 °C min$^{-1}$.

Proton magnetic resonance spectra were recorded at 300.22 MHz on a Bruker Avance 300 spectrometer or at 400 MHz on a JEOL 400EX spectrometer or a Varian 400 MHz spectrometer unless otherwise stated. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; hept, heptet; dd, doublet of doublets; m, multiplet; br, broad and Ar, aromatic. Chemical shifts ($\delta_{^1H}$) are quoted in parts per million and are referenced to the residual solvent peak or to $SiMe_4$ as an internal sample. The multiplicities and general assignments of the spectroscopic data are denoted as: singlet (s), doublet (d), triplet, (t), quartet (q), quintet (quin), doublet of doublets (dd), unresolved multiplet (m), apparent (app), broad (br) and aromatic (Ar). Coupling constants (*J*) are quoted to the nearest 0.1 Hz.

Carbon magnetic resonance spectra were recorded at 75.50 MHz on a Bruker Avance 300 spectrometer or at 100 MHz on a JEOL 400EX spectrometer or at 100 MHz on a Varian 400 MHz spectrometer unless otherwise stated. Chemical shifts ($\delta_{^{13}C}$) are quoted in parts per million and are referenced to the residual solvent peak.

Mass spectra were recorded at the EPSRC National Mass Spectrometry Service Centre, Swansea. Electron impact (EI) and chemical ionisation (CI) analyses were performed in positive ionisation mode. For low resolution measurements ammonia was used as the CI reagent gas, on a Micromass Quattro II triple quadrupole instrument. For high resolution measurements heptacosa (perfluorotributylamine) was used as the EI and CI reference compound, and were performed on the Finnigan MAT900 high resolution double focussing mass spectrometer with tandem ion trap or on a MAT95 high

resolution double focussing mass spectrometer. Both low and high resolution fast atom bombardment (FAB) analyses were performed, in positive or negative ionisation mode, on either a Finnigan MAT900 or a MAT95, using 3-nitrobenzyl alcohol (NOBA) as the matrix liquid.

Elemental analyses were performed with an Exeter analytical, INC. CE-440 elemental analyzer in the Chemistry Department at the University of Bath.

High Performance Liquid Chromatography (HPLC) was performed on TSP Thermo Separation Products spectra series system, which uses chiral column such as Chiralpak AD by Daicel Chemical Ind. Ltd.

Single crystal X-ray diffraction data was collected on a Nonius Kappa CCD machine. Structure determination and refinement were achieved using the SHELX suite of programmes; drawings were produced using ORTEX or MERCURY©.

Analytical thin layer chromatography was carried out using commercially available glass-backed plates coated with Merck Kieselgel 60 $GF_{254}$ or aluminium backed plates coated with Merck or Macherey-Nagel $G/UV_{254}$. Plates were visualised under UV light (at 254 nm) or by staining with potassium permanganate, vanillin or phosphomolybdic acid followed by heating. Flash chromatography was carried out using Merck 60 H silica gel (35-70 μm). Samples were pre-absorbed onto silica or loaded as saturated solvents in an appropriate solvent.

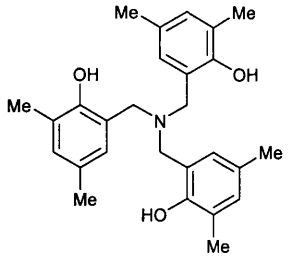
Anhydrous tetrahydrofuran and toluene were obtained by distillation from sodium benzophenone ketyl under nitrogen. Anhydrous dichloromethane and acetonitrile were obtained by distillation from calcium hydride under a nitrogen atmosphere. Petrol refers to the fraction of petroleum ether boiling at 40-60°C. Ether refers to diethyl ether. Solvents were evaporated on a Büchi Rotorvapor.

Unless otherwise stated all commercially available compounds were used as obtained from the chemical suppliers, or purified in accordance with the instructions in D. D. Perrin and W. L. F. Armarego, 'Purification of Laboratory Chemicals' Pergman Press, third edition, 1988, where necessary.

Reactions requiring anhydrous conditions were performed under nitrogen in flame-dried apparatus. All temperatures which are quoted are external.

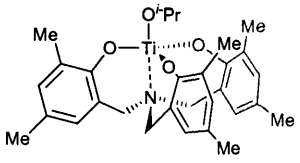
## 5.2 Chapter 2 Experimental

### Tris(2-hydroxy-3,5-dimethylbenzyl) Amine 200[186]



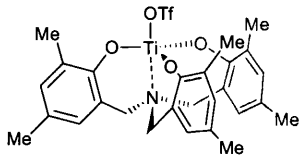

Hexamethylenetetraamine (2.45 g, 17.5 mmol) and paraformaldehyde (3.15 g, 105 mmol) were added to 2,4-dimethylphenol (25.0 mL, 210 mmol) in water (3 mL). The reaction mixture was stirred at reflux for 64 hours, after which the yellow precipitate which had formed was filtered and washed with cold hexane to afford the product as an off-white solid (23.41 g, 80%): $\upsilon_{max}$ /cm$^{-1}$ 858, 1156, 1484, 1608, 2874, 3369; $\delta_H$ (300 MHz, $CDCl_3$) 2.20, 2.21 (18H, 2 × s, both Ar-C*H*$_3$), 3.63 (6H, s, NC*H*$_2$), 4.54 (3H, br s, 3 × ArO*H*), 6.72 (3H, m, 3 × Ar*H*), 6.85 (3H, m, 3 × Ar*H*); $\delta_C$ (75 MHz, $CDCl_3$) 16.3, 20.8 (2 × *C*H$_3$), 56.8 ($CH_2$), 122.1, 125.0, 129.3, 129.5, 131.7, 151.5 (Ar); *m/z* (ES$^+$) 420.2531 ([M-H]$^+$ – $C_{27}H_{33}NO_3$ requires 420.2533) (CI$^+$) 420.3 (100%).

### Amine Tris(phenolate) Titanium *Iso*-propoxide (*rac*)-207




Titanium tetra *iso*-propoxide (3.1 mL, 10 mmol) was added to a suspension of tris(amine) (4.2 g, 10 mmol) in toluene (50 mL) under a nitrogen atmosphere. The resulting yellow solution was heated to reflux and concentrated under vacuum to afford the product as a yellow powder (4.6 g, 88%): mp 193-196 °C (from hexane); (Found: C, 68.8; H, 7.1; N, 2.7; $C_{30}H_{37}NO_4Ti$ requires C, 68.5; H, 7.1; N, 2.6%); $\upsilon_{max}$ /cm$^{-1}$ 862, 1160, 1362, 1379, 1476, 1607, 2853; $\delta_H$ (400 MHz, $CDCl_3$) 1.45 (6H, d, *J* = 6.0 Hz, OCH(C*H*$_3$)$_2$), 2.14, 2.17 (18H, 2 × s, both Ar-C*H*$_3$), 2.75, 3.90 (6H, ABq, *J* = 10.6 Hz, 3 × $CH_2$), 5.13 (hept, *J* = 6.0 Hz, 1H, OC*H*(CH$_3$)$_2$), 6.62 (3H, s, Ar-*H*), 6.78 (3H, s, Ar-*H*); $\delta_C$ (100 MHz, $CDCl_3$) 16.4, 20.7 (2 × *C*H$_3$), 25.7 (CH(*C*H$_3$)$_2$), 58.6 ($CH_2$) 79.8 (*C*H(CH$_3$)$_2$), 123.5, 124.1 (C, Ar), 127.3 (CH, Ar), 129.1 (C, Ar), 130.5 (CH, Ar), 159.4 (C-O, Ar); *m/z* (FAB) 523.5 (M$^+$).

**Titanium Tris(phenolate) Triflate (*rac*)-231**

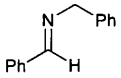



Titanium tris(phenolate) *iso*-propoxide (*rac*)-**207** (5.23g, 10mmol) in toluene was treated with trimethylsilyltriflate (1.8ml, 10mmol), under a nitrogen atmosphere. The resulting red suspension was heated to reflux and concentrated under vacuum to a red/orange solid, which was suspended in hexane and filtered. The residue was washed with hexane and dried under vacuum to afford the product as a red/orange powder (6.05g, 98%): mp (dec.) 285-287°C (from hexane), (Found: C, 54.8; H, 4.9; N, 2.3; $C_{28}H_{30}F_3NO_6STi$ requires C, 54.8; H, 5.0; N, 2.3%); $\upsilon_{max}$ /cm$^{-1}$ 640, 860, 1029, 1160, 1243, 1416, 1477, 1685, 2922; $\delta_{^1H}$ (300 MHz, $CDCl_3$) 2.14, 2.18 (18H, 2 × s, both Ar-C*H*$_3$), 3.09, 4.04 (6H, 2 × s, br, 3 × $CH_2$), 6.70 (3H, s, Ar-*H*), 6.82 (3H, s, Ar-*H*); $\delta_{^{13}C}$ (75 MHz, $CDCl_3$) 16.1, 21.1 (2 × *C*H$_3$), 59.3 ($CH_2$), 123.4, 124.6 (C, Ar), 128.9 (CH, Ar), 132.1 (CH, Ar), 133.1 (C, Ar), 160.9 (C-O, Ar); $\delta_{^{19}F}$ NMR (376 MHz) –78.15 (3F, s, $CF_3$); *m/z* (FAB) 613.5 ($M^+$).

## 5.2.2 General Procedure for the Formation of the Imines used as Dienophiles in the *aza*-Diels Alder Reaction

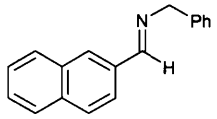
A solution of aldehyde (10 mmol) and amine (10 mmol) in DCM (15 mL) were stirred in the presence of magnesium sulphate (5.0g). After the reaction was deemed complete the reaction mixture was filtered and the solvent removed *in vacuo* to yield the product.

***N*-Benzylidene(phenyl)methanamine 218a**[130]



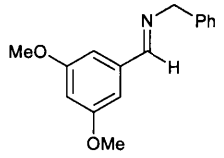

Yellow oil (1.85 g, 95%): $\delta_{^1H}$ (300MHz, $CDCl_3$) 4.89 (2H, s, C*H*$_2$Ph), 7.26-7.55 (8H, m, Ar), 7.81-7.90 (2H, m, Ar), 8.44 (1H, s, C*H*N); $\delta_{^{13}C}$ (75MHz, $CDCl_3$) 60.9 (*C*H$_2$Ph), 127.5, 128.5, 128.8, 129.0, 129.1, 131.3, 136.7, 139.8 (Ar), 168.1 (C=N); *m/z* ($ES^+$) 196.1123 ($[M+H]^+$ – $C_{14}H_{13}N$ requires 196.1121) ($CI^+$) 196.0 $[M+H]^+$ (100%).

**N-(Naphthalen-2-ylmethylene)(phenyl)methanamine 218b**[130]



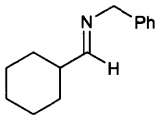

White solid, recrystallised from EtOAc/PE (2.33 g, 95%): $\delta_H$ (300MHz, $CDCl_3$) 4.89 (2H, s, C*H*$_2$Ph), 7.36-7.41 (5H, m, Ar), 7.51-7.58 (2H, m, Ar*H*), 7.83-7.92 (3H, m, Ar*H*), 8.04-8.10 (2H, m, Ar*H*), 8.58 (1H, C*H*N); $\delta_C$ (75MHz, $CDCl_3$) 65.5 (*C*H$_2$Ph), 124.3, 126.9, 127.4, 127.6, 128.3, 128.4, 128.9, 129.0, 130.5, 133.5, 134.2, 135.2, 139.7 (Ar), 162.4 (C=N); *m/z* ($ES^+$) 246.1280 ($[M+H]^+$ – $C_{18}H_{15}N$ requires 246.1277) ($CI^+$) 246.2 $[M+H]^+$ (100%).

**N-(3,5-Dimethoxybenzylidene)(phenyl)methanamine 218c**[130]



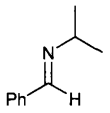

Yellow oil (2.27 g, 89%): $\delta_H$ (300MHz, $CDCl_3$) 3.84 (6H, s, 2 × OC*H*$_3$), 4.87 (2H, s, C*H*$_2$Ph), 6.63 (1H, m, Ar), 7.05 (2H, m, Ar*H*), 7.28-7.38 (1H, m, Ar*H*), 7.39-7.43 (4H, m, Ar*H*), 8.33 (1H, s, C*H*N); $\delta_C$ (75MHz, $CDCl_3$) 55.9 (2 × O*C*H$_3$), 65.4 (*C*H$_2$Ph), 104.0, 106.4, 127.5, 128.5, 129.0, 138.8, 139.7 (Ar), 161.5 (2 × Ar *C*-OCH$_3$), 162.4 (C=N); *m/z* ($ES^+$) 255.1261 ($[M+H]^+$ – $C_{16}H_{17}NO_2$ requires 255.1259) ($CI^+$) 256.2 $[M+H]^+$ (100%).

**N-(Cyclohexylmethylene)(phenyl)methanamine 218d**[130]



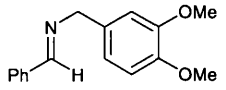

Yellow oil (1.77 g, 88%): $\delta_H$ (300MHz, $CDCl_3$) 1.10-1.41 (5H, m), 1.61-1.95 (5H, m), 2.21-2.34 (1H, m, C*H*C=N), 4.58 (2H, s, C*H*$_2$Ph), 7.21-7.39 (5H, m, Ar*H*), 7.64 (1H, m, C*H*N); $\delta_C$ (75MHz, $CDCl_3$) 25.9, 26.0, 30.1 (*c*-hex), 44.0 (*C*HC=N), 65.4 (*C*H$_2$Ph), 127.2, 128.7, 129.0, 140.0 (Ph), 170.7 (C=N); *m/z* ($ES^+$) 201.1520 ($[M+H]^+$ – $C_{14}H_{19}N$ requires 201.1517) ($CI^+$) 256.2 $[M+H]^+$ (100%).

**N-Benzylidene *iso*-propylamine 218e[130]**



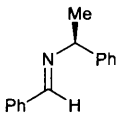
Yellow oil (1.35 g, 92%): $\delta_{^1H}$ (300MHz, $CDCl_3$); 1.19 (6H, d, $J$ = 6.4 Hz, $CH(CH_3)_2$), 3.46 (dsept., $J$ = 0.8, 6.4 Hz, $CH(CH_3)_2$), 7.30-7.35 (3H, m, Ph), 7.62-7.68 (2H, m, Ph), 8.23 (1H, s, CHN); $\delta_{^{13}C}$ (75MHz, $CDCl_3$) 24.6 ($CH(CH_3)_2$), 62.1 ($CH(CH_3)_2$), 128.4, 129.0, 130.8, 136.9 (Ar), 158.7 (C=N); *m/z* ($ES^+$) 148.1121 ($[M+H]^+ - C_{10}H_{13}N$ requires 148.1121) ($CI^+$) 148.1 $[M+H]^+$ (100%).

**N-Benzylidene[3,4-dimethoxyphenyl]methanamine 218f[130]**



Yellow oil (2.45 g, 96%): $\delta_{^1H}$ (300MHz, $CDCl_3$); $\delta_{^{13}C}$ (75MHz, $CDCl_3$) 3.75 (3H, s, $OCH_3$), 3.77 (3H, s, $OCH_3$), 4.65 (2H, s, $CH_2$), 6.72-6.80 (3H, m, Ar), 7.27-7.33 (3H, m, Ar), 7.64-7.71 (2H, m, Ar), 8.26 (1H, s, CHN); $\delta_{^{13}C}$ (75MHz, $CDCl_3$) 56.7 (2 × $OCH_3$), 65.3 ($CH_2$), 114.9, 115.7, 123.1, 128.8, 131.6, 132.8, 139.9 (Ar) 147.9, 149.7 (2 × Ar *C*-$OCH_3$), 161.2 (C=N); *m/z* ($ES^+$) 255.1260 ($[M+H]^+ - C_{16}H_{17}NO_2$ requires 255.1259 $[M+H]^+$ 256.2 (100%).

**(*S*)-N-Benzylidene-1-phenylethanamine 233[130]**



Yellow oil (2.03 g, 97%): $\delta_{^1H}$ (300MHz, $CDCl_3$) 1.68 (3H, d, $J$ = 6.6 Hz, $CH_3$), 4.62 (1H, q, $J$ = 13.2, 6.6 Hz, $CHCH_3$), 7.27-7.34 (1H, m, Ar-H), 7.40-7.54 (6H, m, Ar-H), 7.85-7.88 (2H, m, Ar-H), 8.44 (1H, s, HC=N); $\delta_{^{13}C}$ (75MHz, $CDCl_3$) 25.4 ($CH_3$), 70.2 ($CHCH_3$), 127.1, 127.3, 128.8, 128.9, 129.02, 131.1, 136.9, 145.7 (Ar), 159.9 (C=N); *m/z* ($ES^+$) 210.1277 ($[M+H]^+ - C_{15}H_{15}NO_2$ requires 210.1277) ($CI^+$) 209.2 $[M]^+$ (100%).

### 5.2.3 Optimisation Reactions for the *Aza*-Diels Alder Reaction

Catalyst (*rac*)-**231** (0.042 - 0.21 mmol) was added to a solution of Danishefsky's diene (1.26 mmol) and *N*-benzylidene(phenyl)methanamine **218a** (0.42 mmol) in DCM (1 - 15 mL) at room temperature. The mixture was then stirred for 2 hours before either being quenched with saturated ammonium chloride solution and extracted with DCM or the addition of silica (0.50 g) followed by removal of solvent *in vacuo*. The crude reaction mixture was purified using column chromatography ($SiO_2$, 60:40 EtOAc:PE) to afford the product.

**Table 76**

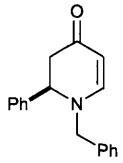
| Entry | Imine /eq. | Diene /eq. | Catalyst mol% | Conc /M | Time | Isolated yield /% | Conv[b] /% |
|---|---|---|---|---|---|---|---|
| 1 | 1 | 1.2 | 100 | 0.03 | <2 min | - | 100 |
| 2 | 1 | 1.2 | 50 | 0.03 | 15 min | 34 | 99 |
| 3 | 1 | 1.2 | 20 | 0.03 | 70 min | 36 | 94 |
| 4[a] | 1 | 1.2 | 10 | 0.03 | 3 h | 35 | 96 |
| 5 | 1 | 1.2 | 10 | 0.03 | 2 h | 35 | 92 |
| 6 | 1 | 1.2 | 1 | 0.03 | 4 h | 18 | 61 |
| 7 | 3 | 1 | 3 | 0.03 | 45 h | 69 | 80 |
| 8 | 3 | 1 | 3 | 0.07 | 23 h | 46 | 100 |
| 9 | 3 | 1 | 3 | 0.42 | 4 h | 72 | 100 |
| 10 | 3 | 1 | 3 | 0.42 | 24 h | 52 | 100 |
| 11 | 1 | 3 | 3 | 0.42 | 45 min | 72 | 65 |
| 12 | 1 | 3 | 10 | 0.42 | 45 min | 69 | 100 |
| 13 | 1 | 3 | 30 | 0.42 | 15 min | 71 | 100 |
| 14 | 1 | 3 | 30 | 0.42 | 100 min | 62 | 100 |
| 15[c] | 3 | 1 | 10 | 0.42 | 2 h | 60 | 90 |
| 16[c] | 3 | 1 | 10 | 0.42 | 15 h | 64 | 95 |
| 17[c] | 1 | 3 | 10 | 0.42 | 45 min | 73 | 100 |
| 18[c] | 1 | 3 | 3 | 0.42 | 45 min | 65 | 65 |
| 19[c] | 1 | 3 | 30 | 0.42 | 20 min | 59 | 100 |

[a] Reaction performed at -78 °C; [b] Conversion measured *via* $^1$H NMR spectroscopic analysis; [c] No aqueous work-up

### 5.2.4 General Procedure for the *Aza*-Diels-Alder Reaction Catalysed by (*rac*)-231

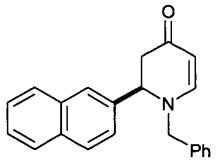
Catalyst (*rac*)-**231** (0.042 mmol) was added to a solution of Danishefsky's diene (1.26 mmol) and the respective imine **218a-f** (0.42 mmol) in DCM (1 mL) at room temperature. The mixture was then stirred for 2 hours before addition of silica (0.50 g) followed by removal of solvent *in vacuo*. The crude reaction mixture was purified using column chromatography ($SiO_2$, 60:40 EtOAc:PE) to afford the product.

**1-Benzyl-2-phenyl-2,3-dihydro-1H-pyridin-4-one 219a**[130]



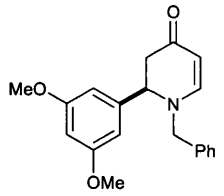

Viscous yellow oil (0.080 g, 73%): $\delta_{^1H}$ (300MHz, $CDCl_3$) 2.60 (1H, dd, $J$ = 8.0, 16.5 Hz, one H-3), 2.77 (1H, dd, $J$ = 7.1, 16.5 Hz, other H-3), 4.04 (1H, d, $J$ = 15.1 Hz, $CH_AH_BPh$), 4.27 (1H, d, $J$ = 15.1 Hz, $CH_AH_BPh$), 4.42 (1H, dd, $J$ = 7.5, 8.0 Hz, H-2), 5.01 (1H, d, $J$ = 7.5 Hz, H-6), 7.04-1.08 (2H, m, Ar), 7.13-7.31 (9H, m, Ar and H-5); $\delta_{^{13}C}$ (75MHz, $CDCl_3$) 44.0 (C-3), 57.7 (C-2), 61.1 ($CH_2Ph$), 99.1 (C-5), 127.5, 128.6, 128.7, 129.3, 129.4, 136.3, 139.0, (Ar), 154.7 (C-6), 190.8 (CO).

**1-Benzyl-2-naphthalen-2-yl-2,3-dihydro-1H-pyridin-4-one 219b**[130]



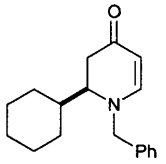

Viscous yellow oil (0.093 g, 71%): $\delta_{^1H}$ (300MHz, $CDCl_3$); 2.71 (1H, dd, $J$ = 8.5, 16.4 Hz, one H-3), 2.81 (1H, dd, $J$ = 7.2, 16.6 Hz, other H-3), 4.06 (1H, d, $J$ = 15.1 Hz, $CH_AH_BPh$), 4.30 (1H, d, $J$ = 15.1 Hz, $CH_AH_BPh$), 4.59 (1H, dd, $J$ = 7.8 Hz, H-2), 5.06 (1H, d, $J$ = 7.7 Hz, H-6), 7.02-7.81 (13H, m, Ar and H-5); $\delta_{^{13}C}$ (75MHz, $CDCl_3$) 44.6 (C-3), 57.7 ($CH_2Ph$), 61.4 (C-2), 99.3 (C-5), 124.9, 126.6, 126.8, 127.0, 128.1, 128.2, 128.3, 129.3, 129.6, 133.5, 133.6 135.0, 136.5 (Ar), 154.7 (C-6), 198.9 (CO).

**1-Benzyl-2-(3,5-dimethoxy-phenyl)-2,3-dihydro-1H-pyridin-4-one 219c**[130]



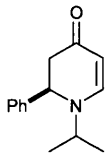

Viscous yellow oil (0.081 g, 60%): $\delta_H$ (300MHz, $CDCl_3$) 2.60 (1H, dd, $J$ = 8.2, 16.5 Hz, one H-3), 2.75 (1H, dd, $J$ = 7.1, 16.5 Hz, other H-3), 3.69 (6H, s, 2 × $CH_3$), 4.09, (1H, d, $J$ = 15.1 Hz, $CH_AH_BAr$), 4.28 (1H, d, $J$ = 15.1 Hz, $CH_AH_BAr$), 4.35 (1H, app. t, $J$ = 7.6 Hz, H-2), 5.01 (1H, d, $J$ = 7.5 Hz, H-6), 6.31-6.34 (3H, m, Ar), 7.07-7.10 (2H, dd, $J$ =1.8, 7.4 Hz, H-5), 7.19-7.34 (3H, m Ar); $\delta_C$ (75MHz, $CDCl_3$) 43.9 (C-3), 55.8 (2 × $OCH_3$), 57.6 ($CH_2Ph$), 61.3 (C-2), 99.1 (C-5), 100.2, 105.5, 128.2, 128.6, 129.3, 136.4, 141.3 (Ar), 161.6 (Ar $C$-$OCH_3$), 154.6 (C-6), 190.8 (CO).

**1-Benzyl-2-cyclohexyl-2,3-dihydro-1H-pyridin-4-one 219d**[130]




Viscous yellow oil (0.063 g, 56%): $\delta_H$ (300MHz, $CDCl_3$) 0.82-1.22, 1.51-1.89 (each 5H, m, $c$-hex), 2.32 (1H, dd, $J$ = 16.7, 2.0 Hz, one H-3), 2.56 (1H, dd, $J$ = 16.7, 7.6 Hz, other H-3), 3.15 (1H, m, H-5), 4.31 (1H, d, $J$ = 14.9 Hz, $CH_AH_BPh$), 4.39 (1H, d, $J$ = 15.4 Hz, $CH_AH_BPh$), 4.83 (1H, d, $J$ = 7.4 Hz, H-6), 7.05 (1H, d, $J$ = 7.3 Hz, H-5), 7.15-7.35 (5H, m, Ar); $\delta_C$ (75MHz, $CDCl_3$) 26.5, 26.7, 29.1, 30.4, 37.4, 39.6 (C-3 and $c$-hex), 59.5 ($CH_2Ph$), 61.3 (C-2), 99.1 (C-5), 127.5, 128.1, 129.1, 137.4 (Ar), 153.8 (C-6), 191.5 (CO).

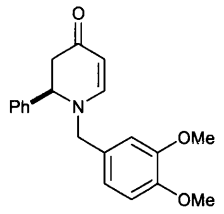
**1-*Iso*-propyl-2-phenyl-2,3-dihydro-1H-pyridin-4-one 219e**[130]




Viscous yellow oil (0.065 g, 72%): $\delta_H$ (300MHz, $CDCl_3$) 1.05 (3H, d, $J$ = 6.6 Hz, one $CH_3$), 1.17 (3H, d, $J$ = 7.0 Hz, other $CH_3$), 2.58 (1H, dd, $J$ = 7.9, 16.4 Hz, one H-3), 2.80 (1, dd, $J$ = 7.0, 16.4 Hz, other H-3), 3.30 (1H, sept, $J$ = 6.7 Hz, $CH(CH_3)_2$), 4.57 (1H, app. t, $J$ = 7.5 Hz, H-2), 5.02 (1H, d, $J$ = 7.7 Hz, H-3), 7.19-7.31 (9H, m, Ar and

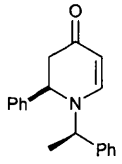
H-5); $\delta_{^{13}C}$ (75MHz, $CDCl_3$) 22.0, 30.1 ($CH(CH_3)_2$), 44.6 (C-3), 53.0 ($CH(CH_3)_2$), 61.5 (C-2), 99.1 (C-5), 127.1, 128.5, 129.4, 140.1, (Ar), 150.4 (C-6), 190.8 (CO).

### 5.2.5 1-(3,5-Dimethoxy-benzyl)-2-phenyl-2,3-dihydro-1H-pyridin-4-one 219f[130]




Viscous yellow oil (0.084 g, 62%): $\delta_{^1H}$ (300MHz, $CDCl_3$) 2.61 (1H, dd, $J$ = 8.2, 16.5 Hz, one H-3), 2.76 (1H, dd, $J$ = 16.5, 7.1 Hz, other H-3), 3.73, 3.81 (each 3H, s, $OCH_3$), 4.01 (1H, d, $J$ = 14.8 Hz, $CH_AH_BAr$), 4.21 (1H, d, $J$ = 14.8 Hz, $CH_AH_BAr$), 4.42 (1H, app. t, $J$ =7.6 Hz, H-2), 5.01 (1H, d, $J$ = 7.7 Hz, H-3), 6.47 (1H, d, $J$ = 1.9 Hz, H-2'), 6.61 (1H, dd, $J$ = 1.9, 8.1 Hz, H-5'), 6.76 (1H, d, $J$ = 8.3 Hz, H-6'), 7.24-7.33 (6H, m, Ph and H-5); $\delta_{^{13}C}$ (75MHz, $CDCl_3$) 44.1 (C-3), 56.3, 56.3 (2 × $OCH_3$), 57.6 ($CH_2Ar$), 61.0 (C-2), 99.0 (C-5), 111.2, 111.6, 120.7, 127.5, 128.4, 128.7, 129.4, 139.1 (Ar), 149.3, 149.6 (2 × Ar $C$-$OCH_3$), 154.5 (C-6), 190.8 (CO).

**2-Phenyl-1-[(*S*)-1-phenylethyl)-2,3-dihydropyridin-4(1H)-one 234**[139]

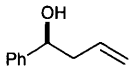



Viscous yellow oil (0.011 g, 10%): (*R,S*)-**234**: $\delta_{^1H}$ (300MHz, $CDCl_3$) 1.39 (3H, d, $J$ = 7.0 Hz, $CH_3$), 2.64 (1H, dd, $J$ = 16.4, 8.9 Hz, one H-3), 2.74 (1H, dd, $J$ = 16.3, 6.3 Hz, other H-3), 4.32-4.40 (1H, m, $CHCH_3$), 4.63 (1H, dd, $J$ = 9.0, 6.6 Hz, H-2), 4.97 (1H, d, $J$ = 7.7 Hz, H-6), 6.98 (1H, d, $J$ = 7.7 Hz, H-5), 7.19-7.35 (10H, m, Ar); (*S,S*)-**234**: $\delta_{^1H}$ (300MHz, $CDCl_3$) 1.50 (3H, d, $J$ = 7.0 Hz, $CH_3$), 2.54 (1H, dd, $J$ = 16.4, 7.0 Hz, one H-3), 2.76 (1H, dd, $J$ = 16.3, 7.1 Hz, other H-3), 4.20 (1H, q, $J$ = 7.1 Hz, H-2), 4.32-4.40 (1H, m, $CHCH_3$), 5.06 (1H, d, $J$ = 7.7 Hz, H-6), 7.19-7.35 (10H, m, Ar) 7.54 (1H, d, $J$ = 7.7 Hz, H-5); (*R,S*)-**234** and (*S,S*)-**234**: $\delta_{^{13}C}$ (75MHz, $CDCl_3$) 19.8 ($CH_3$), 44.6 (C-3), 53.7 (C-2), 63.1 ($CH_2Ph$), 99.3 (C-5), 127.6, 128.4, 128.8, 129.1, 129.7, 136.7, 139.4, (Ar), 153.6 (C-6), 194.8 (CO).

## 5.3 Chapter 3 Experimental

### 5.3.1 Allyltributyltin Addition to Benzaldehyde Catalysed by (*rac*)-231

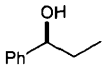
#### 1-Phenylprop-2-en-1-ol 181[146]




Benzaldehyde (0.1 mL, 1 mmol) and allyltributyltin (0.34 mL, 1.1 mmol) were added to a solution of (*rac*)-**231** (0.026 g, 0.05 mmol) in DCM. The solution was stirred for 4 hours before being quenched by the addition of water. The organic layer was washed with water before being dried over $MgSO_4$. The solvent was removed *in vacuo* to yield the crude product as an orange oil. Column chromatography ($SiO_2$, 7:1 PE: EtOAc) resulted in the title product as a yellow oil (0.114 g, 77%): $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 2.10 (1H, br s, CHO*H*), 2.40-2.45 (2H, m, C*H*$_2$CHOH), 4.65 (1H, dd, *J* = 5.7, 7.4 Hz, $CH_2CHOH$), 5.04-5.11 (2H, m, C*H*$_2$=CH), 5.73 (1H, ddt, *J* = 7.2, 10.2, 17.1 Hz, $CH_2$=C*H*), 7.17-7.31 (5H, m, Ar); $\delta_{^{13}C}$ NMR (75MHz, $CDCl_3$ 44.3 (*C*H$_2$CHOH), 73.7 ($CH_2$*C*HOH), 118.8 (*C*H$_2$=CH), 126.2, 128.0, 128.8 (Ar), 134.9 ($CH_2$=*C*H), 144.3 (quat. Ar).

### 5.3.2 Diethyl Zinc Addition to Benzaldehyde Catalysed by (*rac*)-231

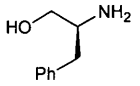
#### 1-Phenyl-propanol 117[150]




A solution of diethyl zinc in hexane (3 mL, 1.0 M, 3 mmol) was added to a solution of (*rac*)-**231** (0.105 g, 0.2 mmol) in DCM (2 mL). This solution was stirred for 10 minutes before being cooled to 0 °C and benzaldehyde (0.1 mL, 1 mmol) was added. Stirring was continued at 0 °C for 6 hours, before being quenched by 1.0 N HCl (4 mL). The aqueous layer was extracted with EtOAc and the combined organic layers were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to yield the crude product as a yellow oil. Column chromatography ($SiO_2$, 7:1 PE: EtOAc) resulted in the title product as a yellow oil (0.104 g, 77%): $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 0.83 (3H, t, *J* = 7.4 Hz, $CH_3$), 1.59-1.81 (2H, m, $CH_2$), 1.96 (1H, br s, CHO*H*), 4.50 (1H, t, *J* = 6.7 Hz, C*H*OH), 7.16-7.30 (5H, m, Ar-*H*); $\delta_{^{13}C}$ NMR (75MHz, $CDCl_3$) 10.6 (*C*H$_3$), 32.3 (*C*H$_2$), 76.4 (*C*HOH), 126.4, 127.9, 128.8 (Ar), 145.0 (quat. Ar).

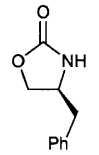
### 5.3.3 Preparation of (*S*)-4-Benzyloxazolidin-2-one[161]

#### (*S*)-2-Amino-3-phenylpropan-1-ol 268[161]




Boron trifluoride-etherate (15.3 mL, 121.2 mmol) was added dropwise to a solution of (*S*)-phenylalanine (20.0 g, 121.0 mmol) in THF (60 mL) in a flame-dried three-necked round bottomed flask equipped with a pressure equalising addition funnel and an 18-inch Vigreux column with a distillation head. The reaction was refluxed for one hour, after which the solid material had completely dissolved. The reaction temperature was then adjusted to just below the reflux point and borane dimethyl sulphide complex (12.7 mL, 133.3 mmol) was added dropwise over 20 minutes. During the addition, hydrogen was evolved and dimethyl sulphide was allowed to distil as it was liberated. The reaction was then refluxed for 6 hours before being cooled to room temperature. A 1:1 mixture of THF/water (15 mL) was added carefully, followed by 5 M sodium hydroxide (90 mL) and the reaction mixture was refluxed for a further 12 hours. The remaining THF was removed *in vacuo* and the resulting slurry was extracted with DCM (5 × 20 mL). The combined organic extracts were washed with brine, dried over sodium sulphate, filtered and concentrated under reduced pressure to afford the title compound, which was recrystallised from hot ethyl acetate as white needles (13.60 g, 74%): $[\alpha]_D^{25}$ -23.5 (c 1.03, ethanol) [lit.,[161] -22.4 (c 1.03, EtOH)]; $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 1.80 (3H, br s, OH, $NH_2$), 2.52 (1H, dd, $J$ = 13.5, 8.5 Hz, $CH_AH_BPh$), 2.80 (1H, dd, $J$ = 13.5, 5.0 Hz, $CH_AH_BPh$), 3.08-3.17 (1H, m, $CHNH_2$), 3.38 (1H, dd, $J$ = 10.5, 7.5 Hz, one $CH_2OH$), 3.64 (1H, dd, $J$ = 10.5, 4.0 Hz, other $CH_2OH$), 7.18-7.34 (5H, m, Ar-*H*); $\delta_{^{13}C}$ NMR (75MHz, $CDCl_3$) 41.2 ($CH_2Ph$), 54.6 ($CHNH_2$), 66.3 ($CH_2OH$), 126.9, 129.0, 129.6, 138.8 (Ar).

#### (*S*)-4-Benzyloxazolidin-2-one 269[161]



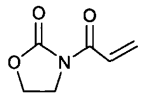

Potassium carbonate (1.250 g, 9.0 mmol) and diethyl carbonate (21.30 g, 180.1 mmol) were added to (*S*)-2-amino-3-phenylpropan-1-ol **269** (13.602 g, 90.1 mmol) in a dry, 100 mL, 3-necked equipped with a pressure equalising addition funnel and an 18-inch

Vigreux column with a distillation head. The reaction was heated to 135-140 °C and ethanol was allowed to distil as it was formed for 2 hours. The reaction was cooled to room temperature, diluted with DCM, and filtered to remove most of the remaining potassium carbonate. The filtrate was washed with sodium bicarbonate and brine, dried ($MgSO_4$) and the solvent was removed *in vacuo* to afford the crude product. Recrystallisation (EtOAC/PE) resulted in the title compound as a white crystalline solid (13.305 g, 83%): $[\alpha]_D^{25}$ -+5.5 (c 1.09, EtOH) [lit.,[161] +4.9 (c 1.10, ethanol)]; $\delta_H$ NMR (300MHz, $CDCl_3$) 2.84 (1H, dd, $J$ = 13.5, 7.0 Hz, $CH_AH_BPh$), 2.91 (1H, dd, $J$ = 13.5 Hz, 7.0 Hz, $CH_AH_BPh$), 4.04-4.17 (2H, m, one H-5, H-4), 4.42 (1H, app t, $J$ = 8.0 Hz, other H-5), 6.12 (1H, br s, N*H*), 7.15-7.37 (5H, m, Ar-*H*); $\delta_C$ NMR (75MHz, $CDCl_3$) 41.8 ($CH_2Ph$), 54.2 (C-4), 70.0 (C-5), 127.6, 128.2, 129.4, 136.3 (Ar), 160.0 (CO).

### 5.3.4 General Procedure for the Formation of the Oxazolidin-2-one Dienophiles

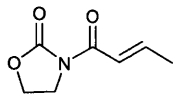
Sodium hydride (1.2 g, 60% dispersion in mineral oil, 30 mmol) was placed in a flame-dried three-necked flask. The material was then washed with anhydrous hexane (2 x 10 mL) and dichloromethane (50 mL) was added. The slurry was then cooled to -15°C before 2-oxazolidinone (1.32 g, 15 mmol) or (*S*)-4-benzyloxazolidin-2-one (2.66 g, 15 mmol) **267** was added. When the vigorous bubbling had ceased the reaction mixture was cooled to -78°C and the appropriate acid chloride (15 mmol) was added drop wise. The solution was then allowed to warm to room temperature and stirred overnight, after which it was filtered through silica and the solvent removed. The resulting solid was then recrystallised from dichloromethane and petrol.

**3-Acryloyloxazolidin-2-one 155a**[187]



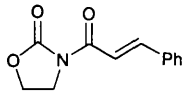
White needles (1.20 g, 57%): $\delta_H$ NMR (300MHz, $CDCl_3$) 4.00-4.07 (2H, m, H-5), 4.36-4.42 (2H, m, H-4), 5.85 (1H, dd, $J$ =10.5, 2.0Hz, *cis*-H-3'), 6.50 (1H, dd, $J$ = 17.5, 1.5 Hz, *trans*-H-3'), 7.43 (1H, dd, $J$ = 17.0, 10.5 Hz, H-2'); $\delta_C$ NMR (75MHz, $CDCl_3$) 43.0 (C-5), 62.5 (C-4), 127.3 (C-2'), 132.2 (C-3'), 153.8 (CO(C-2)), 165.4 (CO(C-1')); HPLC (Daicel Chiralcel AD with 19:1 Hex:IPA) 22.93, (Daicel Chiralcel OD with 9:1 Hex:IPA) 36.33; *m/z* ($ES^+$) 142.0502 ($[M+H]^+$ $C_6H_8NO_3$ requires 142.0499) ($CI^+$) 142.1 $[M+H]^+$ (35%), 159.1 $[M+NH_4]^+$ (100%).

**(*E*)-3-But-2-enoyloxazolidin-2-one 155b**[188]



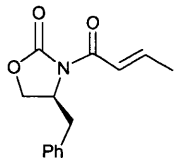
White needles: (1.93 g, 83%): $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 1.94 (3H, d, 5.0Hz, $CH_3$), 4.01-4.08 (2H, m, H-5), 4.37-4.44 (2H, m, H-4), 7.07-7.27 (2H, m, H-3', H-2'); $\delta_{^{13}C}$ NMR (75MHz, $CDCl_3$) 18.9 ($CH_3$), 42.8 (C-5), 62.3 (C-4), 121.8 (C-2'), 147.0 (C-3'), 153.9 (CO(C-2)), 165.5 (CO(C-1)); HPLC (Daicel Chiralcel AD with 19:1 Hex:IPA) $t_r$ = 23.8 min; *m/z* ($ES^+$) 156.0655 ($[M+H]^+$ $C_7H_{10}NO_3$ requires 156.0656) ($CI^+$) 156.1 $[M+H]^+$ (28%), 173.2 $[M+NH_4]^+$ (100%).

**(*E*)-3-(3-Phenylacryloyl)oxazolidin-2-one 155c**[188]



White needles (1.81 g, 43%): $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 4.03-4.11 (2H, m, H-5), 4.35-4.44 (2H, m, H-4), 7.30-7.37 (3H, m, Ph), 7.51-7.60 (2H, m, Ph), 7.79 (1H, d, *J* = 16.0 Hz, H-2'), 7.86 (1H, d, *J* =16.0Hz, H-3'); $\delta_{^{13}C}$ NMR (75MHz, $CDCl_3$) 43.2 (C-5), 62.5 (C-4), 117.0 (C-2'), 129.1, 129.3, 131.1, 134.9 (Ar), 146.7 (C-3'), 154.0 (CO(C-2)), 165.8 (CO(C-1)) ; HPLC (Daicel Chiralcel AD with 19:1 Hex:IPA) $t_r$ = 60.4 min; *m/z* ($ES^+$) 218.0808 ($[M+H]^+$ $C_{12}H_{12}NO_3$ requires 218.0812) ($CI^+$) 218.1 $[M+H]^+$ (100%).

**(*S,E*)-4-Benzyl-3-but-2-enoyloxazolidin-2-one 265**[187]



White solid (2.45 g, 64%), $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 1.99 (3H, d, *J* =5.5 Hz, $CH_3$), 2.80 (1H, dd, *J* =9.5, 13.0 Hz, $CH_AH_BPh$), 3.33 (1H, dd, *J* =3.0, 13.0 Hz, $CH_AH_BPh$), 4.15-4.25 (2H, m, H-5), 4.70-4.77 (1H, m, H-4), 7.19-7.37 (7H, m, Ar-H, H-2', H-3'); $\delta_{^{13}C}$ NMR (75MHz, $CDCl_3$) 19.0 ($CH_3$), 38.3 ($CH_2Ph$), 55.7 (C-5), 66.5 (C-4), 122.2 (C-2'), 127.7, 129.3, 129.9, 135.8 (Ar), 147.4 (C-3'), 154.6 (CO(C-2)), 165.3 (CO(C-1)); HPLC (Daicel Chiralcel AD with 19:1 Hex:IPA) $t_r$ =16.5 min; *m/z* ($ES^+$) 246.1126 ($[M+H]^+$ – $C_{14}H_{15}NO$ requires 246.1125) ($CI^+$) 246.1 $[M+H]^+$ (40%), 263.2 $[M+NH_4]^+$ (100%).

### 5.3.5 Optimisation Reactions for the Diels Alder Reaction

The relevant dienophile **155a-c** (0.5 mmol) and (*rac*)-**231** (0.025 - 0.5 mmol) were stirred together in dichloromethane (2 - 5 mL) at room temperature for 15 minutes. Cyclopentadiene (1.5 mmol) was then added *via* syringe and the reaction mixture was allowed to stir. After the reaction was deemed complete by TLC, the reaction mixture was filtered through a plug of silica and washed with dichloromethane. The solvent and excess diene was removed *in vacuo* to yield the product.

**Table 77**

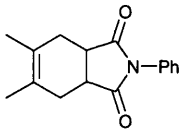
| Entry | Imine | Catalyst mol% | Conc /M | Time | Isolated yield /% | Conv[a] /% |
|---|---|---|---|---|---|---|
| 1[b] | **155a** | 20 | 0.1 | 15 min | 68 | 100 |
| 2 | **155a** | 5 | 0.1 | 45 min | 59 | 100 |
| 3 | **155b** | 5 | 0.1 | 2 h | - | 13 |
| 4 | **155b** | 20 | 0.1 | 2 h | - | 34[c] |
| 5 | **155b** | 20 | 0.1 | 4 h | - | 66[c] |
| 6 | **155b** | 20 | 0.1 | 6 h | - | 94[c] |
| 7 | **155b** | 20 | 0.1 | 8 h | - | 100[c] |
| 8 | **155c** | 20 | 0.1 | 18 h | - | 34 |
| 9 | **155c** | 20 | 0.1 | 48 h | - | 90 |
| 10[d] | **155c** | 20 | 0.1 | 5 h | - | 27 |
| 11[d] | **155c** | 20 | 0.1 | 20 h | - | 42 |
| 12 | **155c** | 100 | 0.1 | 10 h | - | 66 |
| 13 | **155c** | 100 | 0.1 | 18 h | - | 88 |
| 14 | **155c** | 100 | 0.1 | 23 h | 78 | 100 |
| 15 | **155a** | 5 | 0.3 | 30 min | 81 | 100 |
| 16 | **155b** | 20 | 0.3 | 3 h | 87 | 100 |
| 17 | **155c** | 100 | 0.3 | 6 h | 81 | 100 |

[a] Conversion measured *via* $^1$H NMR spectroscopic analysis; [b] With aqueous work-up; [c] Conversion measured by HPLC analysis; [d] Reaction performed at 40 °C

### 5.3.6 General Procedure for the Diels-Alder Reaction Catalysed by (*rac*)-231

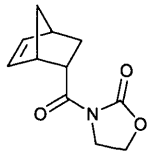
The relevant dienophile **155a-c** or **237** (0.5 mmol) and (*rac*)-**231** (0.025–0.5 mmol) (or $TiCl(O^iPr)_3$ (0.1 mmol) or 2,4-$Me_2C_6H_3OH$ (0.3 mmol) and $TiCl_4$ (0.1 mmol) for dienophile **237**) were stirred together in dichloromethane (2 mL) at room temperature for 15 minutes. The diene (1.5 mmol) was then added *via* syringe and the reaction mixture was allowed to stir. After the reaction was deemed complete by TLC, the reaction mixture was filtered through a plug of silica and washed with dichloromethane. The solvent and excess diene was removed *in vacuo* to yield the product.

**5,6-Dimethyl-2-phenyl-3',4,7,7'-tetrahydro-2*H*-isoindole-1,3-dione 261**[157]




White solid (0.122 g, 96%): $\delta_H$ NMR (300MHz, $CDCl_3$) 1.66 (6H, s, 2 × $CH_3$) 2.33 (2H, br d, $J$ = 13.8 Hz, one H-4, one H-7), 2.46 (2H, br d, $J$ = 14.7 Hz, other H-4, other H-7), 3.12 (2H, m, H-3', H-7'), 7.10 (2H, d, $J$ = 7.5 Hz, Ar-H), 7.32-7.41 (3H, m, Ar-H); $\delta_C$ NMR (75MHz, $CDCl_3$) 19.3 (2 × $CH_3$), 31.0 (H-4, H-7), 40.1 (C-3', C-7'), 126.4, 127.1, 129.2, 129.8 (Ar), 132.2 (C=C), 179.4 (CO).

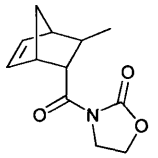
**3-(Bicyclo[2.2.1]hept-2-enecarbonyl)oxazolidin-2-one 157a**[143]




Pale yellow solid (0.084 g, 81%); $\delta_H$ NMR (300MHz, $CDCl_3$) 1.30-1.46 (3H, m, H-5, one H-7), 1.84-1.94 (1H, m, other H-7), 2.88 (1H, m, H-1 or H-4), 3.24 (1H, m, H-4 or H-1), 3.84-3.98 (3H, m, H-6, H-5'), 4.34 (2H, m, H-4'), 5.81 (1H, dd, $J$ =5.5, 3.0Hz, H-3 or H-2), 6.18 (1H, dd, $J$ =5.5, 3.0Hz, H-2 or H-3); $\delta_C$ NMR (75MHz, $CDCl_3$) 29.9 (C-5), 43.2, 43.3, 43.6, 46.5 (C-1, C-6, C-4, C-5'), 50.6 (C-7), 62.3 (C-4'), 132.0, 138.5 (C-3, C-2), 152.7 (CO(C-2')), 175.1 (CO); HPLC (Daicel Chiralcel OD with 9:1 Hex:IPA) $t_r$ = 27.91, 31.21 min; *m/z* ($ES^+$) 208.0971 ($[M+H]^+$ $C_{11}H_{14}NO_3$ requires 208.0968), ($CI^+$) 208.1 $[M+H]^+$ (35%), 225.2 $[M+NH_4]^+$ (100%).

Analysis of the $^1H$ NMR spectrum revealed the product had an *endo*:*exo* ratio of <97:3 and 94% ee.

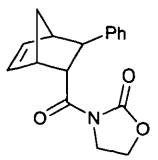
### 3-[5-Methylbicyclo[2.2.1]hept-2-enecarbonyl]oxazolidin-2-one 157b[143]



Colourless oil (0.096 g, 87%); $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 1.06 (3H, d, $J$ = 7 Hz, $CH_3$), 1.40 (1H, dq, $J$ = 3.0, 5.0 Hz, one H-7), 1.63 (1H, d, $J$ = 8.5 Hz, other H-7), 2.03 (1H, m, H-5), 2.47 (1H, m, H-4 or H-1), 3.21 (1H, br s, H-1 or H-4), 3.47, (1H, dd, $J$ = 4.5, 3.5 Hz, H-6), 3.80-4.10 (2H, m, H-5'), 4.34 (2H, t, $J$ = 7.0 Hz, H-4'), 5.71 (1H, dd, $J$ = 5.5, 3.0 Hz, H-3 or H-2), 6.31 (1H, dd, $J$ = 5.5, 3.0 Hz, H-2 or H-3); $\delta_{^{13}C}$ NMR (75MHz, $CDCl_3$) 20.8 ($CH_3$), 36.8 (C-5), 43.4, 47.5, 47.9, 49.9 (C-1, C-6, C-4, C-5'), 51.7 (C-7), 62.3 (C-4'), 131.3, 140.1 (C-3, C-2) 153.9 (CO(C-2')), 174.8 (CO); HPLC (Daicel Chiralcel AD with 19:1 Hex:IPA): 13.61, 15.37; *m/z* ($ES^+$) 239.1389 ($[M+H]^+$ – $C_{12}H_{15}NO_3$ requires 239.1390) ($CI^+$) 239.1 $[M+H]^+$ (100%).

Analysis of the $^1H$ NMR spectrum revealed the product had an *endo*:*exo* ratio of 87:13 and the major *endo* product was obtained in 87% ee.

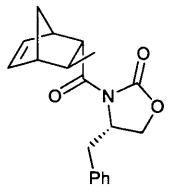
### 3-[5-Phenylbicyclo[2.2.1]hept-2-enecarbonyl]oxazolidin-2-one 157c[143]



Yellow oil (0.123 g, 87%); $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 1.18-1.98 (2H, m, H-7), 2.93, 3.28, 3.40 (each 1H, m, H-1, H-4, H-5), 3.84-4.00 (2H, m, H-5'), 4.13 (1H, dd, H-6), 4.24-4.36 (2H, m, H-4'), 5.86 (1H, dd, $J$ = 5.5, 3.0 Hz, H-3 or H-2), 6.46 (1H, dd, $J$ = 5.5, 3.0 Hz); $\delta_{^{13}C}$ NMR (75MHz, $CDCl_3$) 43.4, 47.2, 47.9, 48.5, 50.1 (C-1, C-6, C-5, C-4, C-5'), 50.4 (C-7), 62.3 (C-4'), 126.5, 128.0, 128.4, 128.9 (Ar), 132.6, 140.6 (C-3, C-2), 153.8 (CO(C-2')), 174.3 (CO); HPLC (Daicel Chiralcel AD with 19:1 Hex:IPA): 17.61, 19.69, 26.41, 39.78; *m/z* ($ES^+$) 301.1549 ($[M+NH_4]^+$ – $C_{17}H_{21}N_2O_3$ requires 301.1549) ($CI^+$) 284.2 $[M+H]^+$ (15%), 301.2 $[M+NH_4]^+$ (100%).

Analysis of the $^1H$ NMR spectrum revealed the product had an *endo*:*exo* ratio of 84:16 and the major *endo* product was obtained in >99% ee.

**(4S)-4-Benzyl-3-(5-methylbicyclo[2.2.1]hept-2-enecarbonyl)oxazolidin-2-one 266**[187]

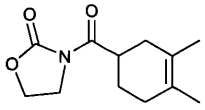



White solid: $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 1.07 (3H, d, $J$ = 7.0Hz, $CH_3$), 1.36-1.41, 1.60-1.67, 2.02-2.11 (each 1H, m, H-1, H-4, H-5), 2.48 (1H, br s, one H-7), 2.60 (1H, dd, $J$ = 9.5, 13.5 Hz, $CH_AH_B$Ph), 2.69 (1H, dd, $J$ = 9.5, 13.5 Hz, $CH_AH_B$Ph), 3.29 (1H, br s, other H-7), 3.45 (1H, dd, $J$ = 3.4, 4.5 Hz, H-6), 4.03-4.14 (2H, m, H-5'), 4.47-4.62 (1H, m, H-4'), 5.75 (1H, dd, $J$ = 3.0, 6.0 Hz, H-3 or H-2), 6.33 (1H, dd, $J$ = 3.0, 6.0 Hz, H-2 or H-3), 7.10-7.28 (5H, m, Ar-H); $\delta_{^{13}C}$ (75MHz, $CDCl_3$) 20.9 ($CH_3$), 37.2 (C-5), 38.5, 47.6, 47.9, 50.1 (C-1, C-6, C-4 and C-5') , 52.2 (C-7), 55.9 ($CH_2$Ph), 66.5 (C-4'), 127.7, 129.3, 129.8, 131.4 (Ar), 135.9, 140.1 (C-3 and C-2), 153.8 (CO(C-2')), 174.8 (CO).

**Table 78**

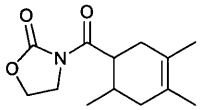
| Entry | Catalyst | Time /h | Mass of 266 /g | Yield /% | *endo*:*exo* | de /% |
|---|---|---|---|---|---|---|
| 1 | (*rac*)-**231** | 3 | 0.151 | 97 | 89 : 11 | 98 |
| 2 | $TiCl(O^iPr)_3$ | 24 | 0.138 | 84 | 79 : 21 | 96 |
| 3 | $2,4\text{-}Me_2C_6H_3OH$, $TiCl_4$ | 2 | 0.115 | 74 | 72 : 28 | 93 |

**3-(3,4-Dimethyl-cyclohex-3-enecarbonyl)-oxazolidin-2-one 264a**[189]




White solid (0.080 g, 72%): $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 1.55 (6H, s, 2 × $CH_3$), 1.80-2.24 (6H, m, H-2, H-5 and H-6), 3.58-3.68 (1H, m, H-1), 3.93-3.99 (2H, m, H-5'), 4.32-4.37 (2H, m, H-4'); $\delta_{^{13}C}$ NMR (75MHz, $CDCl_3$) 19.2, 19.3, 19.1, 19.7 (2 × $CH_3$), 26.6 (C-6), 31.5 (C-2), 33.8 (C-5), 39.4 (C-5'), 43.2 (C-1), 62.3 (C-4'), 124.1, 125.7 (C-3 and C-4), 153.6 (C-2'), 177.1 (CO).

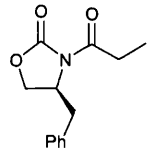
### 3-[3,4,6-Trimethyl-cyclohex-3-enecarbonyl]-oxazolidin-2-one 264b



White solid (0.063 g, 53%): $\upsilon_{max}$ /cm$^{-1}$ 724, 747, 903, 914, 1699, 1780; $\delta_H$ NMR (300MHz, $CDCl_3$) 0.87 (3H, d, $J$ = 6.5 Hz, $CHCH_3$), 1.53 (6H, s, $CH_3C{=}CCH_3$), 1.63-1.80 (1H, m, H-6), 1.89-2.00 (2H, m, H-2 or H-5), 2.06-2.12 (2H, m, H-5 or H-2), 3.55-3.68 (1H, dt, $J$ = 8.0, 10.0 Hz, H-1), 3.95-4.03 (2H, m, H-5'), 4.31-4.36 (2H, t, $J$ = 8.0 Hz, H-4'); $\delta_C$ NMR (75MHz, $CDCl_3$) 19.0 ($CHCH_3$), 19.1, 19.7 ($CH_3C{=}CCH_3$), 31.8 (C-6), 35.8 (C-2), 40.3 (C-5), 43.2 (C-5'), 45.2 (C-1), 62.1 (C-4'), 123.8, 125.5 (C-3 and C-4), 153.7 (CO(C-2')), 177.3 (CO); m/z ($ES^+$) 237.1367 ($[M+H]^+$ $C_{13}H_{19}NO_3$ requires 237.1365) ($CI^+$) 237.1 $[M+H]^+$ (100%).

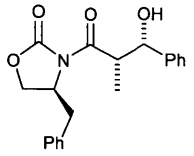
## 5.3.7 Aldol Reaction Catalysed by (*rac*)-231

### (S)-4-benzyl-3-propionyloxazolidin-2-one 270a[161]



A solution of (*S*)-4-benzyloxazolidin-2-one **269** (0.885 g, 5 mmol) in THF (15 mL), under nitrogen was cooled to -78 °C before being treated with $^n$butyl lithium (3.4 mL, 1.45 M, 5 mmol) over a ten minute period. Propionyl chloride (0.48 mL, 5.5 mmol) was then added *via* syringe, and the solution was allowed to stir at −78°C for 30 minutes, before being allowed to warm to room temperature over a 30 minute period. The reaction mixture was then quenched by the addition of saturated aqueous ammonium chloride and was extracted twice with DCM. The combined organic extracts were washed with 1 M NaOH solution and brine, dried over magnesium sulphate, filtered and the solvent was removed *in vacuo*. The resulting pale yellow oil, was allowed to crystallise overnight in a refrigerator. The resulting crystalline solid was washed with a minimum quantity of cold hexane. After filtration and drying the title product was obtained as a colourless crystalline solid (1.032 g, 89%): 1.12 (3H, t, $J$ = 7.2 Hz, $CH_3$), 2.82 (1H, dd, $J$ = 13.3, 9.6 Hz, $CH_AH_BPh$), 2.92 (2H, m, $CH_2CH_3$), 3.23 (1H, dd, $J$ = 13.4, 3.3 Hz, $CH_AH_BPh$), 4.04 (2H, m, H-5), 4.65 (1H, m, H-4), 7.11–7.45 (5H, m, Ar); $\delta_C$ (75MHz, $CDCl_3$) 9.9 ($CH_3$), 27.8 ($CH_2CH_3$), 43.4 ($CH_2Ph$), 46.0 (C-5), 66.9 (C-4), 126.8, 128.2, 129.1, 139.1 (Ar), 153.1 (CO(C-1')), 174.1 (CO(C-2)).

**(*S*)-4-benzyl-3-[(2*R*,3*R*)-3-hydroxy-2-methyl-3-phenylpropanoyl]oxazolidin-2-one 278**[190]



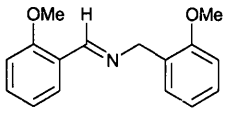
(*S*)-4-Benzyl-3-propionyloxazolidin-2-one **270a** (0.117 g, 0.5 mmol) and DIPEA (0.9 mL, 0.53 mmol) were added to a solution of (*rac*)-**231** (0.307 g, 0.5 mmol) in DCM (3 mL) at 0 °C. Stirring was continued at 0 °C for one hour before benzaldehyde (0.5 mL, 0.5 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 24 hours. After which it was filtered through silica and the solvent was removed. Column chromatography yielded the product as a clear oil (0.058 g, 34% yield, 42% conversion): $\delta_{^1H}$ (300MHz, $CDCl_3$) 1.12 (3H, d, $J$ = 7.9 Hz, $CH_3$), 2.74 (1H, dd, $J$ = 13.4, 9.5 Hz, C$H_A$H$_B$Ph), 3.11 (1H, br s, OH), 3.21 (1H, dd, $J$ = 13.4, 3.4 Hz, CH$_A$$H_B$Ph), 3.92-4.10 (3H, m, H-5, C$H$CH$_3$), 4.52 (1H, m, H-4), 5.01 (1H, m, C$H$OH), 7.11–7.38 (10H, m, ArH); $\delta_{^{13}C}$ (75MHz, $CDCl_3$) 11.4 ($CH_3$), 38.1 ($CH_2$Ph), 45.0 ($CH$($CH_3$)), 55.5 (C-5), 66.6 (C-4), 74.2 ($CH$OH), 126.5, 127.8, 127.9, 128.7, 129.4, 129.8 (Ar), 135.4, 141.7 (quat. Ar), 153.3 (CO(C-1)), 177.1 (CO).

## 5.4 Chapter 4 Experimental

### 5.4.1 General Procedure for the Formation of Imines

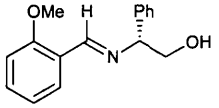
A solution of amine (1 eq.) and aldehyde (1 eq.) in ethanol was stirred with molecular sieves for 26 hours. The mixture was filtered through celite, washed with ethanol and the filtrate was evaporated to dryness to yield the crude product.

***N*-(2-Methoxybenzylidene)(2-methoxyphenyl)methanamine 282**[191]



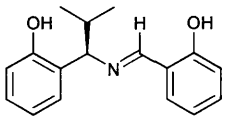

Clear oil (2.50 g, 98%): $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 3.87 (3H, s, one $OCH_3$), 3.89 (3H, s, other $OCH_3$), 4.85 (2H, s, $CH_2$), 6.89-7.04 (4H, m, Ar-H), 7.24-7.43 (3H, m, Ar-H), 8.08 (1H, dd, $J$ = 1.9, 7.5 Hz, 1H, Ar-H), 8.89 (1H, s, *H*C=N); $\delta_{^{13}C}$ NMR (75MHz, $CDCl_3$) 55.8, 55.9 (2 × O*C*$H_3$), 60.1 (*C*$H_2$N), 110.6, 11.4, 120.9, 121.2, 125.3, 127.9, 128.4, 128.6, 129.6, 132.2 (Ar), 157.5, 158.8, 159.2 (2 × Ar *C*-$OCH_3$ and C=N).

**(*R*)-2-[(2-Methoxybenzylidene)-amino]-2-phenylethanol 285**[168]



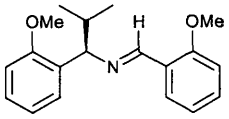

Yellow solid (2.50 g, 98%): $\upsilon_{max}$ /$cm^{-1}$ 3429, 2841, 1636; $\delta_{^1H}$ NMR (300MHz, $C_6D_6$) 1.40 (1H, br s, OH), 3.27 (3H, s, $OCH_3$), 3.86-4.04 (2H, m, C*H*$_2$OH), 4.48 (1H, dd, $J$ = 8.0, 4.0 Hz, C*H*Ph), 6.51 (1H, d, $J$ = 8.5 Hz, Ar-H), 6.96 (1H, t, $J$ = 7.5 Hz, Ar-H) 7.10-7.24 (4H, m, Ar-H), 7.51 (2H, d, $J$ = 7.5 Hz, Ar-H), 8.48 (1H, dd, $J$ = 8.0, 2.0 Hz, Ar-H), 9.08 (1H, s, *H*C=N); $\delta_{^{13}C}$ NMR (75MHz, $C_6D_6$) 55.2 ($OCH_3$), 68.6 (*C*$H_2$OH), 77.8 (*C*HPh), 111.5, 121.3, 125.6, 127.8, 128.2, 128.4, 129.0, 132.5, 142.4 (Ar), 158.4, 159.3 (Ar *C*-$OCH_3$, C=N); *m/z* ($ES^+$) 256.1332 ($[M+H]^+$ $C_{16}H_{18}NO_2$ requires 256.1332) ($CI^+$) 256.1 $[M+H]^+$ (100%).

**(*R*)-*N*-(2-Hydroxybenzylidene)-1-(2-hydroxyphenyl)-2-methylpropan-1-amine 325**




Yellow powder (0.197 g, 77%): mp 150-151 °C; $[\alpha]_D^{25}$ -198.4 (c 0.61, $CHCl_3$); $\upsilon_{max}$ /$cm^{-1}$ 1458, 1488, 1634, 3399; $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 0.90 (3H, d, *J* = 6.8 Hz, one $CH_3$), 1.00 (3H, d, *J* = 6.8 Hz, other $CH_3$), 2.44 (1H, app. sext. *J* = 20.2, 6.9 Hz, C*H*$(CH_3)_2$), 4.28 (1H, d, *J* = 7.9 Hz, C*H*CH$(CH_3)_2$), 6.78-6.98 (4H, m, Ar-H), 7.10-7.14 (1H, m, Ar-H), 7.23-7.35 (3H, m, Ar-H), 8.35 (1H, s, *H*C=N); $\delta_{^{13}C}$ NMR (75MHz, $CDCl_3$) 19.8, 20.4 (2 × *C*$H_3$), 33.5 (*C*H$(CH_3)_2$), 76.3 (*C*HCH$(CH_3)_2$), 116.5, 118.3, 118.4, 120.7, 121.6, 128.1, 128.7, 129.4, 132.3, 133.6 (Ar), 153.9, 164.0, 165.1 (2 × Ar *C*-OH, C=N); *m/z* ($ES^+$) 270.1487 ($[M+H]^+$ $C_{17}H_{19}NO_2$ requires 270.1489), ($CI^+$) 270.1 $[M+H]^+$ (100%).

**(*R*)-*N*-(2-Methoxybenzylidene)-1-(2-hydroxyphenyl)-2-methylpropan-1-amine 326**

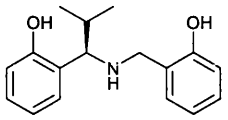



Yellow oil (2.85 g, 96%): $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 0.76 (3H, d, *J* = 6.8 Hz, one $CH_3$), 0.84 (3H, d, *J* = 6.6 Hz, other $CH_3$), 2.15 (1H, app sext., *J* = 6.8 Hz, C*H*$(CH_3)_2$), 3.74 (6H, s, 2 × $OCH_3$), 4.44 (1H, d, *J* = 7.2 Hz, C*H*CH$(CH_3)_2$), 6.76 (2H, ddd, *J* = 8.1, 5.4, 0.9 Hz, Ar-H), 6.83-6.91 (2H, m, Ar-H), 7.09 (1H, td, *J* = 8.1, 7.5, 1.7 Hz, Ar-H), 7.25 (1H, ddd, *J* = 8.3, 1.9, 0.9 Hz, Ar-H), 7.56 (1H, dd, *J* = 7.4, 1.7 Hz, Ar-H), 7.98 (1H, dd, *J* = 7.5, 1.5 Hz, Ar-H), 8.67 (1H, s, *H*C=N); $\delta_{^{13}C}$ NMR (75MHz, $CDCl_3$) 19.8, 20.5 (2 × $CH_3$), 33.7 (*C*H$(CH_3)_2$), 56.8, 57.2 (2 × $OCH_3$), 58.7 (*C*HCH$(CH_3)_2$), 113.7, 114.4, 120.6, 121.9, 123.2, 126.8, 129.6, 130.2, 132.9 (Ar) 158.7, 160.4, 161.1 (2 × Ar *C*-OH, C=N); *m/z* ($ES^+$) 297.1732 ($[M+H]^+$ $C_{19}H_{23}NO_2$ requires 297.1732), ($CI^+$) 297.2 $[M+H]^+$ (100%).

### 5.4.2 Reduction of Imines

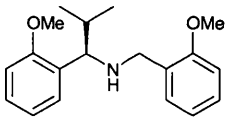
A solution of imine **318** or **319** in methanol was treated with sodium borohydride (3 equivalents) and stirred for 20 minutes. The reaction mixture was quenched with 1.0M sodium hydroxide and the product was extracted with diethyl ether. The organic layer was washed with brine, dried with sodium sulphate and the solvent removed to yield the product.

**(*R*)-*N*-(2-Hydroxybenzyl)-1-(2-hydroxyphenyl)-2-methylpropan-1-amine 324**




Brown oil (0.45 g, 56%): $[\alpha]_D^{25}$ +17.2 (c 0.99, $CHCl_3$); $\upsilon_{max}$ /$cm^{-1}$ 1259, 1458, 1491, 1494, 3349; $\delta_H$ NMR (300MHz, $CDCl_3$) 0.71 (3H, d, $J$ = 6.8 Hz, one $CH_3$), 0.90 (3H, d, $J$ = 6.6 Hz, one $CH_3$), 1.91-2.02 (1H, m, C*H*$(CH_3)_2$), 3.36 (1H, d, $J$ = 7.2 Hz, C*H*CH$(CH_3)_2$), 3.51 (1H, d, $J$ = 13.2 Hz C$H_A$H$_B$Ar), 3.83 (1H, d, $J$ = 13.2 Hz, CH$_A$*H*$_B$Ar), 6.35 (3H, br s, 2 × OH and NH), 6.72-7.20 (8H, m, Ar-H); $\delta_{13C}$ NMR (75MHz, $CDCl_3$) 13.7, 20.3 (2 × $CH_3$), 33.5 (*C*H$(CH_3)_2$), 48.8 ($CH_2$Ar), 68.9 (*C*HCH$(CH_3)_2$), 116.1, 116.9, 119.5, 120.5, 124.5, 124.7, 126.7, 129.4, 130.7, 130.9 (Ar), 155.9, 157.9 (Ar *C*-$OCH_3$); *m/z* ($ES^+$) 271.1573 ($[M+H]^+$ – $C_{17}H_{21}NO_2$ requires 271.1572), ($CI^+$) 271.2 $[M+H]^+$ (100%).

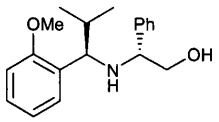
**(*R*)-*N*-(2-Methoxybenzyl)-1-(2-methoxyphenyl)-2-methylpropan-1-amine 299**




Clear oil (1.24 g, 86%): $[\alpha]_D^{25}$ +15.2 (c 1.05, $CHCl_3$); $\upsilon_{max}$ /$cm^{-1}$ 1244, 1369, 1384, 1689, 2870, 3063, 3341; $\delta_H$ NMR (300MHz, $CDCl_3$) 0.68 (3H, d, $J$ = 6.8 Hz, one $CH_3$), 0.87 (3H, d, $J$ = 6.6 Hz, one $CH_3$), 1.82-1.94 (1H, m, C*H*$(CH_3)_2$), 2.00 (1H, br s, N*H*), 3.38 (1H, d, $J$ = 13.4 Hz, C$H_A$H$_B$Ar), 3.58 (1H, d, $J$ = 13.4 Hz, CH$_A$*H*$_B$Ar), 3.69-3.75 (7H, m, 2 × $OCH_3$, C*H*CH$(CH_3)_2$), 6.73-6.90 (4H, m, Ar-H), 7.07-7.20 (3H, m, Ar-H), 7.31 (1H, dd, $J$ = 1.7, 7.5 Hz, Ar-H); $\delta_{13C}$ NMR (75MHz, $CDCl_3$) 19.7, 20.3 (2 × $CH_3$), 33.8 (*C*H$(CH_3)_2$), 47.9 ($CH_2$Ar), 55.5, 55.6 ($OCH_3$ and *C*HCH$(CH_3)_2$), 110.5, 110.7, 120.6, 120.7, 127.5, 127.6, 128.2, 128.5, 129.1, 130.3 (Ar), 158.1, 158.4 (Ar *C*-$OCH_3$); *m/z* ($ES^+$) 300.1955 ($[M+H]^+$ – $C_{19}H_{26}NO_2$ requires 300.1958), 300.3 $[M+H]^+$ (100%).

### 5.4.3 Addition of *Iso*-Propyl Lithium to (*R*)-2-[(2-Methoxybenzylidene)-amino]-2-phenylethanol[168]

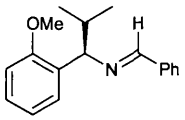
#### (*R*)-2-[(*R*)-1-(2-Methoxy-phenyl)-2-methyl-propylamino]-2-phenyl ethanol 288




A solution of imine **285** (2 mmol) in THF (12 mL) was solidified in liquid $N_2$ before *iso*-propyl lithium (5.7 mL, 0.7 M, 4 mmol) was added *via* syringe. The solution stirred at -85°C for 6 hours, after which, it was brought to 0°C and ammonium chloride (sat., 5 mL) was added carefully, followed by ether (5 mL). The organic layer was separated and the basified aqueous layer (1N NaOH) was extracted with ether (3 × 15 mL). The combined ether layers were washed, dried, filtered, and then passed through a silica plug. The solvent was evaporated *in vacuo* to yield the product as a yellow oil (0.4956 g, 83%, 96% de): $[\alpha]_D^{25}$ -33.0 (c 1, $CHCl_3$); $\upsilon_{max}$ /$cm^{-1}$ 1240, 1365, 1491, 1600, 2960, 3355; $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 0.64 (3H, d, $J$ = 6.8 Hz, one $CH_3$), 1.05 (3H, d, $J$ = 6.6 Hz, other $CH_3$), 1.96 (1H, m, C*H*$(CH_3)_2$), 2.51 (1H, br s, OH), 3.41 (1H, d, $J$ = 5.5 Hz, C$H_A$H$_B$OH), 3.44 (1H, s, C*H*Ph), 3.46 (1H, d, $J$ = 5.5 Hz, C$H_A$H$_B$OH), 3.54 (3H, s, $OCH_3$), 3.67 (1H, dd, $J$ = 14.5, 6.2 Hz, C*H*CH$(CH_3)_2$), 6.59 (1H, app d, $J$ = 8.1 Hz, Ar-H), 6.76 (1H, td, $J$ = 7.4, 1.0 Hz, Ar-H), 6.93-7.10 (7H, m, Ar-H); $\delta_{^{13}C}$ NMR (75MHz, $CDCl_3$) 20.9 (2 × $CH_3$), 33.4 (*C*H$(CH_3)_2$), 55.3 ($OCH_3$), 62.0 (*C*HCH$(CH_3)_2$), 64.6 ($CH_2OH$), 110.8, 120.6, 127.4, 127.5, 128.1, 128.5, 129.5, 142.8 (Ar), 157.7 (Ar *C*-$OCH_3$); *m/z* ($ES^+$) 300.1958 ($[M+H]^+$ $C_{19}H_{26}NO_2$ requires 300.1958) ($CI^+$) 300.2 $[M+H]^+$ (100%).

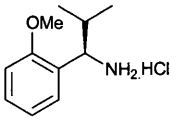
### 5.4.4 Deprotection of (*R*)-2-[[(*R*)-1-(2-Methoxy-phenyl)-2-methyl-propylamino]-2-phenyl ethanol[192]

#### Step One – Formation of (*R*)-*N*-Benzylidene-1-(2-methoxyphenyl)-2-methylpropan-1-amine 294




Lead (IV) acetate (0.518 g, 1.17 mmol) was added to a solution of 2-[1-(2-methoxy-phenyl)-2-methyl-propylamino]-2-phenyl-ethanol **288** (0.350 g, 1.17 mmol) in DCM (1.5 mL) and methanol (3 mL) under ice cooling. After stirring for 5 minutes the reaction mixture was neutralised by the addition of sodium bicarbonate (sat., 10 mL). The resulting insoluble impurities were removed by filtration through celite and were washed with DCM (2 × 10 mL), the organic layer was then separated and the aqueous layer was extracted with DCM (2 × 10 mL). The combined organic layers were dried over magnesium sulphate, filtered, and evaporated *in vacuo* to afford the crude imine as a yellow oil ( 0.303 g, 96%): $[\alpha]_D^{25}$ -105.4 (c 1.18, $CHCl_3$); $\upsilon_{max}$ /cm$^{-1}$ 1241, 1585, 1599, 1645, 2960; $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 0.77 (3H, d, $J$ = 6.8 Hz, one $CH_3$), 0.85 (3H, d, $J$ = 6.6 Hz, other $CH_3$), 2.17 (1H, app. dsept, $J$ = 6.8 Hz, C*H*($CH_3$)$_2$), 3.75 (3H, s, $OCH_3$), 4.42 (1H, d, $J$ = 7.2 Hz, C*H*CH($CH_3$)$_2$), 6.78 (1H, dd, $J$ = 0.9, 8.1 Hz, Ar H-3), 6.90 (1H, ddd, $J$ = 0.9, 7.5 Hz, Ar H-5) 7.11 (1H, ddd, $J$ = 1.7, 7.5, 13.9 Hz, Ar H-4), 7.26-7.32 (3H, m, Ph-H), 7.55 (1H, dd, $J$ = 1.8, 7.6 Hz, Ar H-6), 7.66-7.74 (2H, m, Ph-H), 8.24 (1H, s, *H*C=N); $\delta_{^{13}C}$ NMR (75MHz, $CDCl_3$) 19.6, 20.2 (2 × *C*$H_3$), 34.4 (*C*H($CH_3$)$_2$), 55.8 (O*C*$H_3$), 63.7 (*C*HCH($CH_3$)$_2$), 110.7, 120.9, 127.6, 128.6, 130.2, 137.2, 156.9 (Ar), 160.2 (C=N); *m/z* ($ES^+$) 267.1627 ($[M+H]^+$ - $C_{18}H_{21}NO$ requires 267.1623), ($CI^+$) 267.2 $[M+H]^+$ (100%).

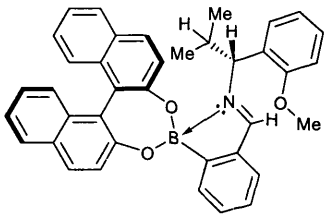
#### Step Two – Formation of (*R*)-1-(2-Methoxyphenyl)-2-methylpropan-1-amine Hydrochloride 290·HCl [168]




The crude benzylidene imine **294** was treated with 6M HCl (50 mL) and THF (15 mL) and stirred at room temperature for 1 hour and then on a steam bath for a further 45 minutes. The reaction mixture was extracted with ether and the aqueous layer was evaporated to yield the hydrochloride salt of the amine as a yellow oil (0.191 g, 78%):

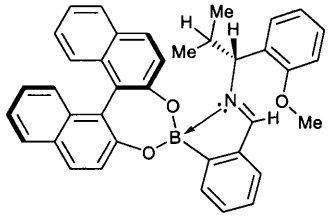
$\upsilon_{max}$ /cm$^{-1}$ 1242, 1465, 1490, 1641, 3415; $\delta_{^1H}$ NMR (300MHz, $D_2O$) 0.69 (3H, d, $J$ = 6.78 Hz, one CH(C$H_3$)$_2$), 1.04 (3H, d, $J$ = 6.41 Hz, other CH(C$H_3$)$_2$), 2.23-2.40 (1H, m, C$H$(CH$_3$)$_2$), 3.81 (3H, s, OCH$_3$), 4.04 (1H, d, $J$ = 9.80 Hz, C$H$NH$_2$), 6.98 (1H, t, $J$ = 7.54 Hz, ArH), 7.06 (1H, d, $J$ = 6.78 Hz, ArH), 7.21 (1H, dd, $J$ = 1.51, 7.54 Hz, ArH), 7.38 (1H, dt, J = 1.88, 7.16 Hz, ArH); $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 0.72 (3H, d, $J$ = 6.78 Hz, one CH(C$H_3$)$_2$), 1.04 (3H, d, $J$ = 6.41 Hz, other CH(C$H_3$)$_2$), 2.25-2.37 (1H, m, C$H$(CH$_3$)$_2$), 3.69 (3H, s, OCH$_3$), 4.12-4.21 (1H, m, C$H$NH$_2$), 6.76-6.85 (2H, m, Ar), 7.12-7.30 (3H, m, Ar); $\delta_{^{13}C}$ NMR (75MHz, $D_2O$) 19.1, 19.3 (2 × CH$_3$), 30.8 (*C*H(CH$_3$)$_2$), 55.8, 59.9 (OCH$_3$ and *C*HNH$_2$), 112.3, 121.3, 126.4, 130.2, 130.9 (Ar); *m/z* (ES$^+$) 180.1383 ([M-Cl]$^+$ $C_{11}H_{18}NO$ requires 180.1384), (EI$^+$) 180.1 [M-Cl]$^+$ (100%).

### 5.4.5 Standard for the Determination of Enantiomeric Excess of (*R*)-1-(2-Methoxyphenyl)-2-methylpropan-1-amine Hydrochloride with (*rac*)-BINOL



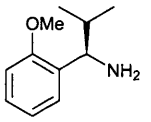

(*R*)-1-(2-Methoxyphenyl)-2-methylpropan-1-amine hydrochloride **290·HCl** (0.018 g, 0.1 mmol) was treated with caesium carbonate (0.036 g, 0.11 mmol), 2-formyl boronic acid (0.016 g, 0.11 mmol), and (*rac*)-BINOL (0.032 g, 0.11 mmol) at room temperature under a nitrogen atmosphere. The mixture was stirred in the presence of 4Å molecular sieves for 30 minutes before a sample was taken for NMR analysis: $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) Enantiomer A: 0.62 (3H, d, $J$ = 6.6 Hz, one CH(C$H_3$)$_2$), 1.25 (3H, d, $J$ = 6.4 Hz, other CH(C$H_3$)$_2$), 2.40-2.54 (1H, m, C$H$(CH$_3$)$_2$), 2.99 (3H, s, OCH$_3$), 4.70 (1H, d, $J$ = 11.1 Hz, C$H$CH(CH$_3$)$_2$), 6.65 (1H, d, $J$ = 7.7 Hz, Ar-H), 6.80-8.0 (19H, m, Ar), 8.73 (1H, s, *H*C=N); Enantiomer B: 0.71 (3H, d, $J$ = 6.8 Hz, one CH$_3$), 0.97 (3H, d, $J$ = 6.4 Hz, other CH$_3$), 2.56-2.72 (1H, m, C$H$(CH$_3$)$_2$), 3.40 (3H, s, OCH$_3$), 5.02 (1H, d, $J$ = 10.2 Hz, C$H$CH(CH$_3$)$_2$), 6.25 (1H, d, $J$ = 8.7 Hz, Ar-H), 6.80-8.0 (19H, m, Ar), 8.69 (1H, s, *H*C=N).

### 5.4.6 Determination of Enantiomeric Excess of (*R*)-1-(2-Methoxyphenyl)-2-methylpropan-1-amine Hydrochloride with (*S*)-BINOL




(*R*)-1-(2-Methoxyphenyl)-2-methylpropan-1-amine hydrochloride **290·HCl** (0.018 g, 0.1 mmol) was treated with caesium carbonate (0.036 g, 0.11 mmol), 2-formyl boronic acid (0.016 g, 0.11 mmol), and (*rac*)-BINOL (0.032 g, 0.11 mmol) at room temperature under a nitrogen atmosphere. The mixture was stirred in the presence of 4Å molecular sieves for 30 minutes before a sample was taken for NMR analysis affording the product in 90% de with data as above.

#### (*R*)-1-(2-Methoxyphenyl)-2-methylpropan-1-amine 290[168]

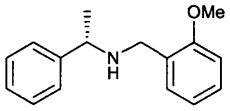



A solution of amine (*R*)-**290·HCl** (1.03 g, 0.48 mmol) in ethyl acetate (5 mL) was treated with triethylamine (0.73 mL, 0.53 mmol). The resulting precipitate was filtered off and the filtrate was evaporated *in vacuo*, resulting in (*R*)-1-(2-methoxyphenyl)-2-methylpropan-1-amine as a brown oil which formed a beige foam under vacuum, (0.076 g, 98%): $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 0.71 (3H, d, $J$ = 6.6 Hz, one $CH_3$), 0.95 (3H, d, $J$ = 6.4 Hz, other $CH_3$), 2.03 (1H, m, C*H*$(CH_3)_2$), 3.73 (3H, s, $OCH_3$), 3.92 (1H, br d, $J$ = 7.7 Hz, C*H*CH$(CH_3)_2$), 4.27 (2H, br s, $NH_2$), 6.78 (1H, d, $J$ = 8.3 Hz, Ar-H), 6.84 (1H, t, $J$ = 7.4 Hz, Ar-H), 7.14 (1H, t, $J$ = 7.5 Hz, Ar-H), 7.22 (1H, d, $J$ = 7.3 Hz, Ar-H); $\delta_{^{13}C}$ NMR (75MHz, $CDCl_3$) 19.7, 20.4 (2 × $CH_3$), 33.4 (*C*H$(CH_3)_2$), 55.7, 57.5 (*C*HCH$(CH_3)_2$, $OCH_3$), 111.0, 120.9, 128.5, 128.6, 131.1 (Ar) 157.3 (Ar *C*-$OCH_3$).

### 5.4.7 General Procedure for One Pot Direct Aminations of Primary Amines[172]

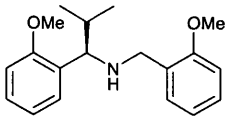
A mixture of amine or amine hydrochloride (1 eq.) and aldehyde (1 eq.) in DCE (0.3 M) was treated with sodium triacetoxyborohydride (1.4 eq.). The reaction mixture was then stirred under a nitrogen atmosphere and monitored by TLC. When the reaction was deemed complete the reaction was quenched with saturated sodium bicarbonate and the crude product was extracted with EtOAc. The organic layer was dried over magnesium sulphate, filtered and the solvent removed *in vacuo* to yield the crude product. Where hydrochloride salts were used 1.1 equivalents of triethylamine were added.

#### (*S*)-*N*-(2-Methoxybenzyl)-1-phenylethanamine 297[193]




Clear oil (2.36 g, 89%): $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 1.25 (3H, d, $J$ = 6.6 Hz, $CHCH_3$), 3.49 (1H, d, $J$ = 13.4 Hz, $CH_AH_BAr$), 3.66 (1H, d, $J$ = 13.8 Hz, $CH_AH_BAr$), 3.65-3.72 (1H, m, $CHCH_3$), 3.70 (3H, s, $OCH_3$), 6.75 (1H, app. d, $J$ = 8.1 Hz, Ar-H), 6.80 (1H, td, $J$ = 7.3, 0.9 Hz, Ar-H), 7.05-7.29 (7H, m, Ar-H); $\delta_{^{13}C}$ NMR (75MHz, $CDCl_3$) 25.0 ($CHCH_3$), 47.7 ($CH_2Ar$), 55.6, 57.6 ($OCH_3$ and $CHCH_3$), 110.7, 120.8, 127.2, 127.3, 128.6, 128.8, 129.0, 130.4, 146.2 (Ar), 158.2 (Ar $C$-$OCH_3$); *m/z* ($ES^+$) 242.1542 ($[M+H]^+ - C_{16}H_{20}NO$ requires 242.1539), ($CI^+$) 242.2 $[M+H]^+$ (100%).

#### (*R*)-*N*-(2-Methoxybenzyl)-1-(2-methoxyphenyl)-2-methylpropan-1-amine 299

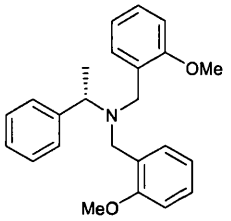



Clear oil (1.32 g, 88%) with data as above (see Section 5.4.2).

### 5.4.8 General Procedure for One Pot Direct Aminations of Secondary Amines

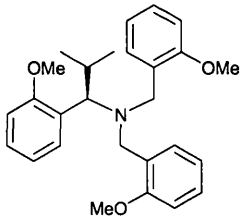
A mixture of amine or amine hydrochloride (1 eq.) and aldehyde (1 eq.) in DCE (0.3 M) was treated with sodium triacetoxyborohydride (1.4 eq.) and acetic acid (1 eq.). The reaction mixture was then stirred under a nitrogen atmosphere and monitored by TLC. When the reaction was deemed complete the reaction was quenched with saturated sodium bicarbonate and the crude product was extracted with EtOAc. The organic layer was dried over magnesium sulphate, filtered and the solvent removed *in vacuo* to yield the crude product.

**(*S*)-*N*,*N*-Bis(2-methoxybenzyl)-1-phenylethanamine 298**




Clear oil (2.857 g, 86%): mp 69-71 °C; $[\alpha]_D^{25}$ -70.0 (c 1, $CHCl_3$); $\upsilon_{max}$ /$cm^{-1}$ 1240, 1379, 1600, 2836, 2937; $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 1.37 (3H, d, $J$ = 7.0 Hz, $CHCH_3$), 3.45 (2H, d, $J$ = 15.1 Hz, $CH_AH_BAr$), 3.69 (1H, d, $J$ = 15.3 Hz, $CH_AH_BAr$), 3.68 (6H, s, $OCH_3$), 3.89 (1H, q, $J$ = 6.8, 13.6 Hz, $CHCH_3$), 6.71 (2H, dd, $J$ = 8.1, 0.8 Hz, Ar-H), 6.85 (2H, td, $J$ = 8.5, 0.9 Hz, Ar-H), 7.19 (3H, qt, $J$ = 7.2, 14.9, 1.7 Hz, Ar-H), 7.21 (2H, td, $J$ = 7.2, 1.3 Hz, Ar-H), 7.37 (2H, app d, $J$ = 7.7 Hz, Ar-H), 7.56 (2H, dd, $J$ = 7.5, 1.7 Hz, Ar-H); $\delta_{^{13}C}$ NMR (75MHz, $CDCl_3$) 14.2 ($CHCH_3$), 47.9 (2 × $CH_2Ar$), 55.6, 57.6 ($OCH_3$ and $CHCH_3$), 110.4, 120.9, 126.8, 127.6, 128.2, 128.3, 129.2, 129.9, 144.4 (Ar), 158.1 (Ar C-$OCH_3$); *m/z* ($ES^+$) 362.2115 ($[M+H]^+$ $C_{24}H_{28}NO_2$ requires 362.2114), ($CI^+$) 362.3 $[M+H]^+$ (100%).

**(*R*)-*N*,*N*-Bis(2-methoxybenzyl)-1-(2-methoxyphenyl)-2-methylpropan-1-amine 300**




Pale yellow solid (1.13 g, 61%): mp 159-161 °C; $[\alpha]_D^{25}$ -58.0 (c 1, $CHCl_3$); $\upsilon_{max}$ /$cm^{-1}$ 1236, 1586, 1598, 2832, 2954; $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 0.63 (3H, d, $J$ = 6.4 Hz, one

$CH_3$), 1.35 (3H, d, $J$ = 6.4 Hz, other $CH_3$), 2.44 (1H, app. sept., $J$ = 6.8 Hz, C*H*$(CH_3)_2$), 3.41 (2H, d, $J$ = 16.0 Hz, 2 × C$H_A$H$_B$Ar), 3.46 (3H, s, $OCH_3$), 3.64 (2H, d, $J$ = 16.0 Hz, 2 × CH$_A$$H_B$Ar), 3.72 (6H, s, 2 × $OCH_3$), 4.05 (1H, br d, $J$ = 10.7 Hz, C*H*CH$(CH_3)_2$), 6.78 (2H, dd, $J$ = 8.1, 0.9 Hz, Ar-H), 6.85 (1H, dd, $J$ = 8.1, 0.8 Hz, Ar-H), 6.94 (2H, td, $J$ = 7.5, 1.1 Hz, Ar-H), 7.05 (1H, td, $J$ = 7.4, 1.0 Hz, Ar-H), 7.16 (2H, td, $J$ = 7.9, 1.5 Hz, Ar-H), 7.21-7.33 (2H, m, Ar-H) 7.79 (2H, app. d, $J$ = 7.2 Hz, Ar-H); $\delta_{^1H}$ NMR (300MHz, $C_6D_5CD_3$) 0.52 (3H, d, $J$ = 6.6 Hz, one $CH_3$), 1.29 (3H, d, $J$ = 6.6 Hz, other $CH_3$), 2.20 (1H, app sept. $J$ = 6.2 Hz, C*H*$(CH_3)_2$), 2.92 (3H, s, $OCH_3$), 3.03 (6H, s, 2 × $OCH_3$), 3.48 (2H, d, 2 × C$H_A$H$_B$Ar), 3.65 (2H, d, 2 × CH$_A$$H_B$Ar), 4.13 (1H, d, $J$ = 10.7 Hz, C*H*CH$(CH_3)_2$), 6.27 (2H, dd, $J$ = 7.9, 0.9 Hz, Ar-H), 6.37 (1H, dd, $J$ = 9.2, 0.9 Hz, Ar-H), 6.67-6.91 (6H, m, Ar-H), 7.08 (1H, dd, $J$ = 7.5, 1.5 Hz, Ar-H), 7.81 (2H, app d, $J$ = 6.4 Hz, Ar-H); $\delta_{^{13}C}$ NMR (75MHz, $CDCl_3$) 21.4, 21.6 (2 × $CH_3$), 29.7 (*C*H$(CH_3)_2$), 47.9 (*C*$H_2$Ar), 55.0, 55.3 (3 × $OCH_3$), 77.3 (*C*HCH$(CH_3)_2$), 109.9, 110.5, 120.2, 120.7, 127.0, 127.2, 127.8, 128.9, 129.8 (Ar), 157.9, 159.3 (Ar *C*-$OCH_3$); *m/z* ($ES^+$) 420.2537 ($[M+H]^+ - C_{27}H_{34}NO_3$ requires 420.2533), 420.4 $[M+H]^+$ (5%), 256.2 (10), 163.1 (100), 121.2 (90%).

### 5.4.9 Attempted Demethylation of Methyl Phenyl Ether (*R*)-300

#### Aluminium Bromide[173]

Methyl phenyl ether (*R*)-**300** (0.042 g, 0.1 mmol) in toluene (0.5 mL) was added to a stirred solution of aluminium bromide (0.117 g, 0.44 mmol) in toluene (0.5 mL) at room temperature. Stirring continued for 20 hours, being the reaction mixture was added to saturated sodium bicarbonate solution (0.2 mL) at 0 °C. The mixture was filtered through celite before being extracted with EtOAc (4 × 5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and the solvent removed to yield the crude product as a brown oil. The $^1$H NMR spectrum revealed a mixture of cleavage products, with demethylated tris(phenol) (*R*)-**279** being present in very small amounts, though isolation proved difficult.

#### Aluminium Chloride[124]

Methyl phenyl ether (*R*)-**300** (0.042 g, 0.1 mmol) was added to a solution of aluminium chloride (0.067 g, 0.5 mmol) in toluene (0.6 mL). The reaction mixture was then stirred at reflux for 5 hours, before being added to saturated sodium bicarbonate solution (1 mL) at 0 °C. The reaction mixture was then filtered through celite, before being extracted with EtOAc (4 × 5 mL). The combined organic layers were dried over

$Na_2SO_4$, filtered, and the solvent was removed *in vacuo*. The $^1H$ NMR spectrum revealed a mixture of cleavage products.

#### Titanium(IV) Chloride

A solution of methyl phenyl ether (*R*)-**300** (0.04 g, 0.096 mmol) in DCM (1 mL) was treated with titanium(IV) chloride (0.05 mL, 0.48 mmol or 0.01 mL, 0.096 mmol) at -78 °C. The reaction was allowed to warm to room temperature and stirred for 2 hours. The solvent was then removed to yield the crude product. The $^1H$ NMR spectrum revealed a mixture of cleavage products.

#### Titanium(IV) *iso*-Propoxide

A solution of methyl phenyl ether (*R*)-**300** (0.04 g, 0.096 mmol) in DCM (1 mL) was treated with titanium(IV) *iso*-propoxide (0.03 mL, 0.096 mmol) at -78 °C. The reaction was allowed to warm to room temperature and stirred for 2 hours. The solvent was then removed to yield the crude product. The $^1H$ NMR spectrum revealed a mixture of cleavage products.

#### Trimethylsilyl iodide in Acetonitrile[176]

A solution of methyl phenyl ether (*R*)-**300** (0.02 g, 0.05 mmol) in acetonitrile (0.8 mL) and trimethylsilyl iodide (0.07 mL, 0.5 mmol) was stirred at reflux for 8 hours. The reaction was then quenched by the addition of saturated $Na_2S_2O_3$ solution and was extracted with chloroform (3 × 5 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$ solution and water, before being dried over $Na_2SO_4$, filtered and the solvent removed. The $^1H$ NMR spectrum revealed the recovery of starting material.

#### Treatment with Sodium Ethanethiolate in refluxing DMF[177,178]

A 0.5 M solution of NaSEt in DMF was prepared as follows: ethanethiol (0.06 mL, 0.7 mmol) was added to an ice cooled stirring suspension of sodium hydride in DMF (1.4 mL), under a nitrogen atmosphere and was stirred at room temperature for 15 minutes. 0.6 mL of this solution was added to methyl phenyl ether (*R*)-**300** (0.02 g, 0.05 mmol) and the resulting solution was heated at an oil bath temperature of 115-120 °C under a nitrogen atmosphere. The reaction was monitored by TLC and after 19 hours the cooled reaction mixture was acidified with 10% HCl and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with 10% aq. NaOH (3 × 5 mL) and water before being dried with $Na_2SO_4$, filtered and the solvent removed *in vacuo* to yield the starting material. The chilled basic aqueous washings were acidified with 10% HCl and

extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with water (2 × 5 mL) and dried over $Na_2SO_4$. Filtration and evaporation yield the crude reaction mixture. The $^1H$ NMR spectrum revealed some by-products, but no demethylated product tris(phenol) (*R*)-**279**.

#### Nickel Chloride and Zinc[179]

A mixture of nickel chloride (0.006 g, 0.05 mmol), zinc (0.01 g, 0.15 mmol) and methyl phenyl ether (*R*)-**300** (0.02 g, 0.05 mmol) was stirred in toluene at reflux for four days under a nitrogen atmosphere. The resulting solution was quenched by the addition of water (10 mL) and was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent removed. The $^1H$ NMR spectrum revealed the recovery of starting material.

#### Boron Trichloride and Tetra-$^n$Butylammonium iodide[180]

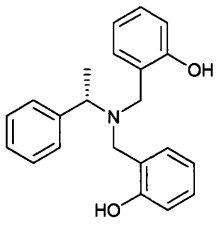
A solution of methyl phenyl ether (*R*)-**300** (0.02 g, 0.05 mmol) and tetra-$^n$-butylammonium iodide in DCM (0.8 mL) under a nitrogen atmosphere was treated with boron trichloride at -78 °C over two minutes. After five minutes the solution was warmed to 0 °C and was stirred for 2 hours. The reaction mixture was quenched with iced water and stirred for 30 minutes, diluted with saturated sodium bicarbonate solution and extracted with DCM. The combined organic layers were dried, concentrated, and purified. The $^1H$ NMR spectrum revealed the possible formation of a boron complex of methyl phenyl ether (*R*)-**300**.

#### Microwave with Methanesulphonic Acid[181]

Methyl phenyl ether (*R*)-**300** (0.02 g, 0.05 mmol) was treated in a microwave with methanesulphonic acid for 30s at 125W and 150 °C. The product was extracted by washing with EtOAc after neutralisation with 4 M NaOH. The $^1H$ NMR spectrum of the acidic solution revealed the presence of the protonated amine (*R*)-**322**. The $^1H$ NMR spectrum of the neutralised solution revealed the recovery of starting material.

### Demethylation of Methyl Phenyl Ethers with boron tribromide

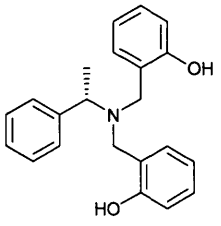
**(*S*)-*N*,*N*-Bis(2-hydroxybenzyl)-1-phenylethanamine 305**




To a solution of amine **298** (1 g, 2.74 mmol) in DCM (80 mL) at -78 °C under a nitrogen atmosphere, was added a solution of boron tribromide in DCM (1.0 M, 22.1 mL, 22.1 mmol). The solution was stirred for 20 hours, after which it was stirred with saturated sodium bicarbonate solution until neutral pH was reached. The reaction mixture was then washed with brine and the organic layer was dried over sodium sulphate, filtered and the solvent removed *in vacuo*. The resulting brown oil was triturated with hexane to yield the title product as a brown solid (m = 0.68 g, 74%): mp 83-85 °C; $[\alpha]_D^{25}$ -40.0 (c 1, $CHCl_3$); $\upsilon_{max}$ /$cm^{-1}$ 1255, 1380, 1610, 2853, 3341; $\delta_H$ NMR (300MHz, $CDCl_3$) 1.79 (3H, d, $J$ = 7.1 Hz, $CH_3$), 3.74 (2H, d, $J$ = 13.0 Hz, $CH_AH_BAr$), 4.16 (2H, d, $J$ = 12.6 Hz, $CH_AH_BAr$), 4.51 (1H, q, $J$ = 7.2 Hz, $CHCH_3$), 5.10 (2H, br s, 2 × OH), 6.72-7.01 (4H, m, Ar-H), 7.11-7.45 (9H, m, Ar-H); $\delta_{13C}$ NMR (75MHz, $CDCl_3$) 19.8 ($CH_3$), 49.8 ($CH_2Ar$), 63.4 ($CH(CH_3)$), 116.5, 120.2, 122.8, 128.9, 129.3, 129.6, 130.8, 137.4 (Ar), 156.7 (Ar C-OH); *m/z* ($ES^+$) 333.1733 ($[M+H]^+ - C_{22}H_{23}NO_2$ requires 333.1729), 333.2 $[M+H]^+$ (100%).

## 5.4.10 Demethylation of Methyl Phenyl Ethers with aluminium tribromide

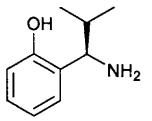
**(*S*)-*N*,*N*-Bis(2-hydroxybenzyl)-1-phenylethanamine 305**




A solution of amine **298** (0.5 g , 1.38 mmol) in toluene (25 mL) was added drop-wise to a solution of aluminium tribromide (1.22 g, 4.56 mmol) in toluene (10 mL). The solution was stirred for 20 hours, after which it was added to saturated sodium bicarbonate solution at 0 °C. The solid aluminium salts were removed *via* filtration

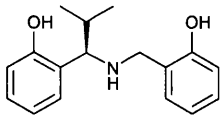
through celite and washed with EtOAc. The organic layer was dried over sodium sulphate, filtered and the solvent removed *in vacuo*. The resulting brown oil was triturated with hexane to yield the title product as a brown solid (m = 0.1 g, 22%) with data as above.

**2-{[*R*]-1-Amino-2-methylpropyl}phenol 323**[168]




A solution of (*R*)-1-(2-methoxyphenyl)-2-methylpropan-1-amine **290** (0.211 g, 1.18 mmol) in toluene (5 mL) was added to aluminium bromide (3.4 eq., 1.068 g, 4.0 mmol) in a round-bottomed flask under a nitrogen atmosphere. The yellow solution was stirred for 20 hours at room temperature, after which it was added to saturated aqueous sodium bicarbonate solution (20 mL) at 0 °C and was extracted with ethyl acetate (15 mL × 4). The combined organic layers were dried over sodium sulphate, filtered, and the solvent was removed *in vacuo*. The yellow was dissolved in ethyl acetate (5 mL) and acetic acid (0.07 mL, 1.18 mmol) was added. The resulting precipitate was dissolved by the addition of methanol (1.5 mL) and heating the mixture to reflux. The solution was allowed to cool to room temperature and further cooled to 0 °C by standing in ice. A white precipitate was obtained and filtered before being dissolved in ethyl acetate (3 mL). Saturated aqueous sodium bicarbonate (15 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (6 mL × 3). The combined organic layers were dried over sodium sulphate, filtered, and the solvent was evaporated under reduced pressure, to yield the product as a yellow oil (0.084 g, 43%): $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 0.77 (3H, d, $J$ = 7.0 Hz, one $CH_3$), 0.94 (3H,d, $J$ = 6.6 Hz, other $CH_3$), 1.97 (1H, app oct, $J$ = 6.8 Hz, C*H*$(CH_3)_2$), 3.73 (1H, d, $J$ = 7.2 Hz, C*H*CH$(CH_3)_2$), 6.68 (1H, td, $J$ = 7.3, 1.1 Hz, Ar-H), 6.75 (1H, dd, $J$ = 8.1, 0.9 Hz, Ar-H), 6.83 (1H, dd, $J$ = 7.5, 1.7 Hz, Ar-H), 7.07 (1H, ddd, $J$ = 0.9, 8.1, 1.7 Hz, Ar-H); $\delta_{^{13}C}$ NMR (75MHz, $CDCl_3$) 18.0, 18.7 (2 × $OCH_3$), 32.3 (*C*H$(CH_3)_2$), 62.0 (*C*HCH$(CH_3)_2$), 116.1, 117.4, 124.8, 127.3, 128.2 (Ar), 156.8 (Ar C-$OCH_3$).

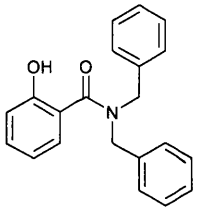
**(*R*)-*N*-(2-Hydroxybenzyl)-1-(2-hydroxyphenyl)-2-methylpropan-1-amine 324**



A solution of (*R*)-*N*-(2-methoxybenzyl)-1-(2-methoxyphenyl)-2-methylpropan-1-amine **299** (0.150 g, 0.5 mmol) in toluene (2 mL) was added to aluminium bromide (3.4 eq., 0.453 g, 1.7 mmol) in toluene (1 mL) in a round-bottomed flask under a nitrogen atmosphere. The yellow solution was stirred for 20 hours at room temperature, after which it was added to saturated aqueous sodium bicarbonate solution (15 mL) at 0 °C and was extracted with ethyl acetate (10 mL × 4). The combined organic layers were dried over sodium sulphate, filtered, and the solvent was removed *in vacuo* to yield the product as a brown oil (0.152 g, 67%) with data identical to that described previously (see Section 5.4.2).

## 5.4.11 Preparation of Amide

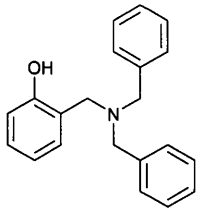
**N,N-Dibenzyl-2-hydroxybenzamide 339[194]**



To a cooled stirred solution of dibenzylamine (0.09 mL, 0.45 mmol), salicylic acid (0.063 g, 0.45 mmol), HOBt (0.06 g, 0.45 mmol) in DME (1.2 mL) was added a solution of DCC (0.093 g, 0.45 mmol) in DME (0.8 mL). Stirring was continued at room temperature for 30 minutes, before the resulting dicyclohexyurea precipitate was filtered off and washed with a small amount of ethyl acetate. The filtrate was diluted with ethyl acetate, extracted with saturated sodium bicarbonate (2 mL), dried and concentrated *in vacuo*. Column chromatography ($SiO_2$, 9:1 PE:EtOAc) resulted in the product as a white solid (0.061 g, 43%): $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 4.61 (4H, s, 2 × C*H*$_2$Ph), 6.66 (1H, td, *J* = 7.7, 1.1 Hz, one Ar-H), 6.96 (1H, dd, *J* = 8.9, 1.2 Hz, one Ar-H), 7.15-7.34 (12H, m, Ar-H), 9.72 (1H, br s, O*H*); $\delta_{^{13}C}$ NMR (75MHz, $CDCl_3$) 50.0 (2 × C*H*$_2$Ph), 117.6, 118.6, 119.1, 127.8, 128.2, 129.4 (Ar), 133.3, 136.5 (quat. Ar), 159.4 (Ar C-OH), 172.9 (C=O).

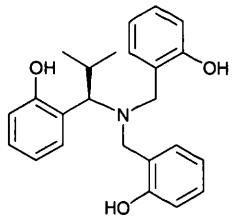
### 5.4.12 Reduction of Amide

**2-{[Dibenzylamino]methyl}phenol 340**




To a solution of *N,N*-dibenzyl-2-hydroxybenzamide **339** (0.025 g, 0.08 mmol) in THF (1.5 mL) was added lithium aluminium hydride in THF (1.0M, 0.39 mL, 0.39 mmol) at room temperature. The suspension was heated to reflux and stirred for 12 hours. After cooling to 0 °C the reaction mixture was quenched with water and filtered through celite with washing with ethyl acetate. The filtrate was extracted with ethyl acetate and the combined organic layers were washed with brine and dried over magnesium sulphate. The solvent was removed *in vacuo* to yield the product as a white solid (0.013 g, 56%): $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 3.52 (4H, s, 2 × $CH_2$Ph), 3.64 (2H, s, $CH_2$Ar), 6.71 (1H, td, $J$ = 7.4, 1.1 Hz, Ar-H), 6.93 (1H, dd, $J$ = 7.5, 1.3, Ar-H), 7.08 (1H, td, $J$ = 7.9, 1.5 Hz, Ar-H), 7.15-7.34 (11H, m, Ar-H); $\delta_{^{13}C}$ NMR (75MHz, $CDCl_3$) 48.9 ($CH_2$Ar), 60.4 (2 × $CH_2$Ph), 114.8, 121.8, 123.4, 128.0, 128.6, 129.1, 130.9, 136.4 (Ar), 155.8 (Ar C-OH).

### 5.4.13 Formation of (*R*)-*N,N*-Bis(2-hydroxybenzyl)-1-(2-methoxyphenyl)-2-methylpropan-1-amine 279 *via* Cyclic Aminol Ether




(*R*)-*N*-(2-Hydroxybenzyl)-1-(2-hydroxyphenyl)-2-methylpropan-1-amine **324** (0.120 g, 0.44 mmol) was dissolved in dichloromethane (5 mL) and 2-hydroxybenzaldehyde (0.24 mL, 2.21 mmol), (1*S*)-(+)-camphorsulphonic acid (0.005 g, 0.022 mmol), and 4Å molecular sieves were added. The mixture was allowed to stir at room temperature for 24 hours, after which it was filtered and the solvent and excess aldehyde were removed under reduced pressure. This afforded a mixture of cyclic aminol ethers **344** and **345** (0.105 g, 64%) which were used without further purification. Thus, they were dissolved in acetonitrile (2 mL) and cooled to -40 °C under a nitrogen atmosphere. Sodium cyanoborohydride (0.07 g, 1.12 mmol) was added, followed by the addition of chloro-

trimethylsilane (0.14 mL, 1.12 mmol) portionwise over 5 minutes. The reaction was stirred for 30 minutes before being quenched with saturated potassium carbonate solution. The reaction mixture was then allowed to warm to room temperature and stirred for one hour before being extracted with dichloromethane and water. The organic layer was washed with brine, dried over magnesium sulphate, filtered and the solvent removed to yield the crude product. The impurities were triturated with hexane, to afford the title product as a brown glass (m = 0.012 g, 11%): $\delta_{^1H}$ NMR (300MHz, $CDCl_3$) 0.72 (3H, d, $J$ = 6.8 Hz, one $CH_3$), 0.91 (3H, d, $J$ = 6.6 Hz, other $CH_3$), 1.90-2.01 (1H, m, C*H*$(CH_3)_2$), 3.36 (1H, d, $J$ = 7.4 Hz, C*H*$CH(CH_3)_2$), 3.51 (1H, d, $J$ = 13.2 Hz, C$H_A$$H_B$Ar), 3.82 (1H, d, $J$ = 13.2 Hz, $CH_A$$H_B$Ar), 5.45 (3H, br s, OH), 6.71-7.11 (12H, m, Ar-H).

# CHAPTER 6:
# *References*

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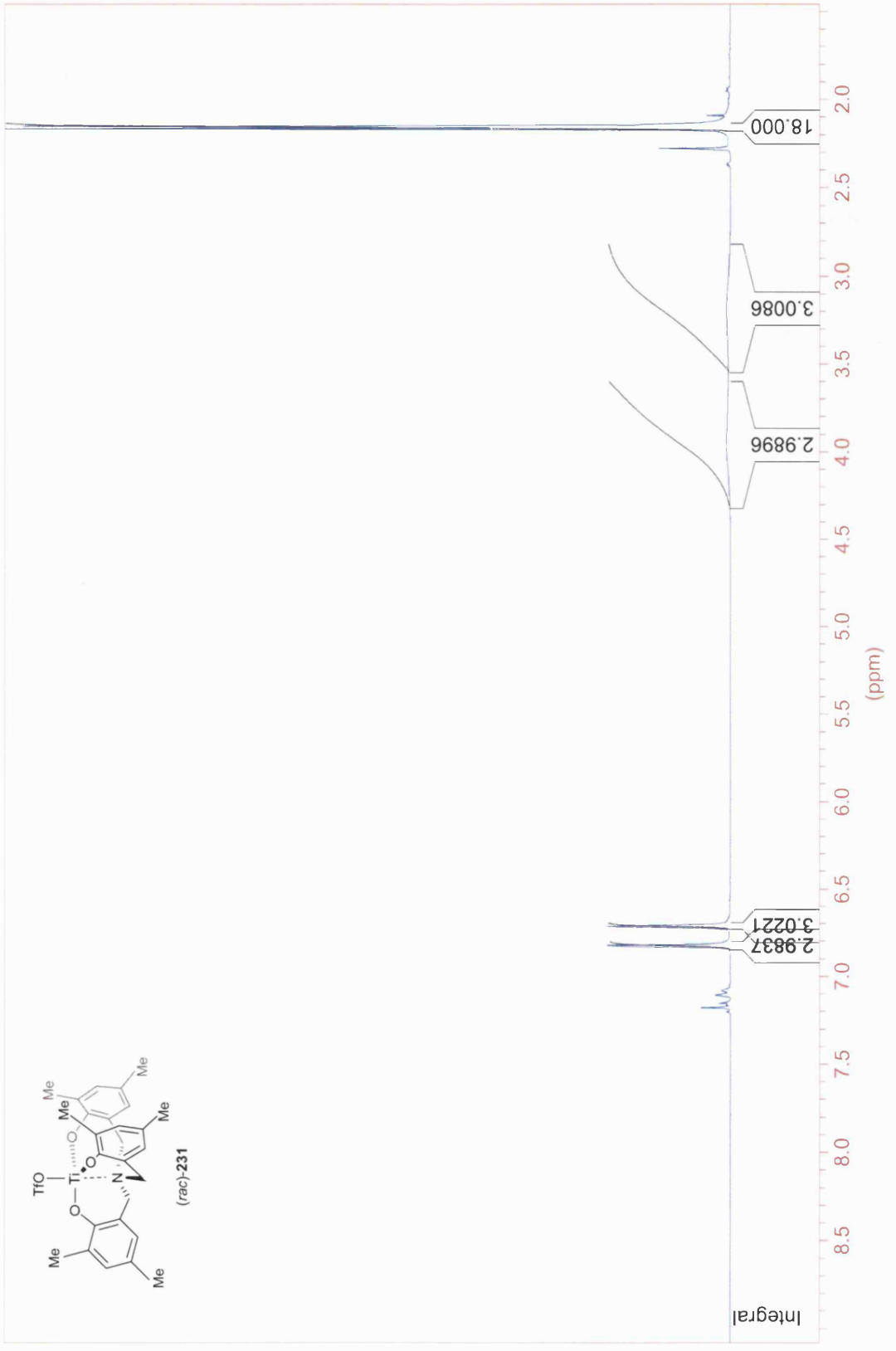
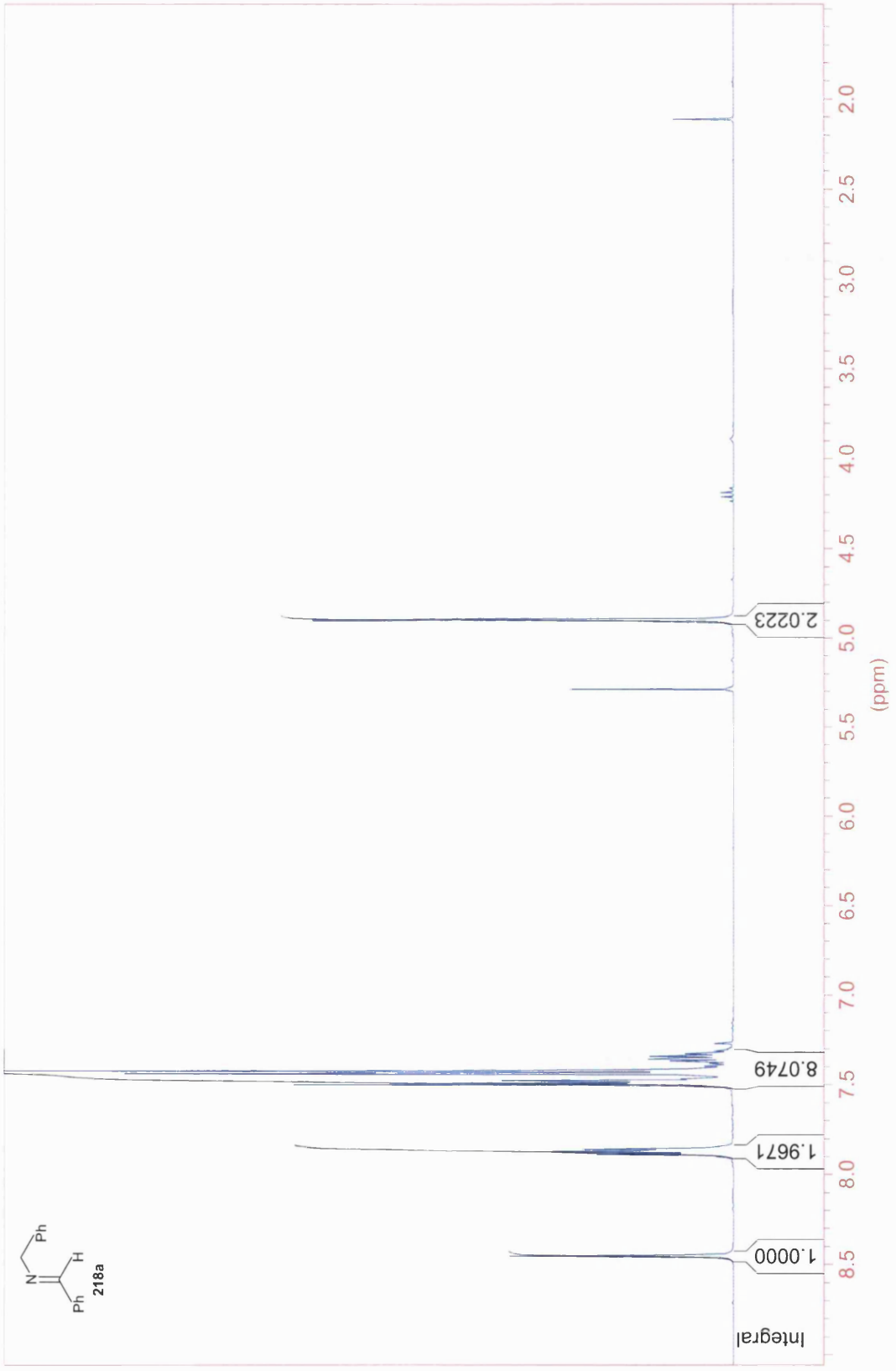
# APPENDIX 1:
# $^1H$ NMR Spectra

# 1 $^1$H NMR SPECTRA

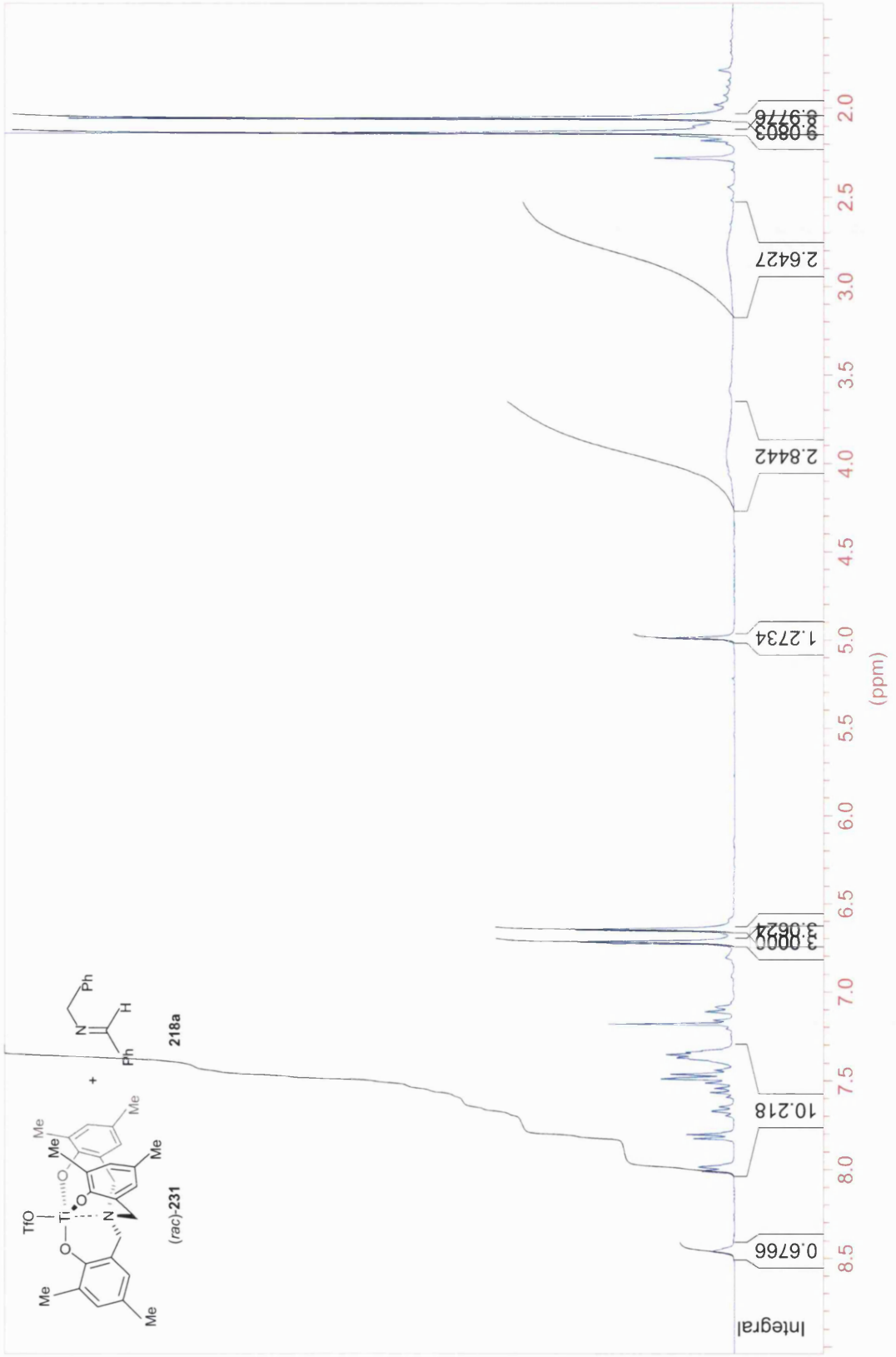
## 1.1 $^1$H NMR Spectrum of (*rac*)-231



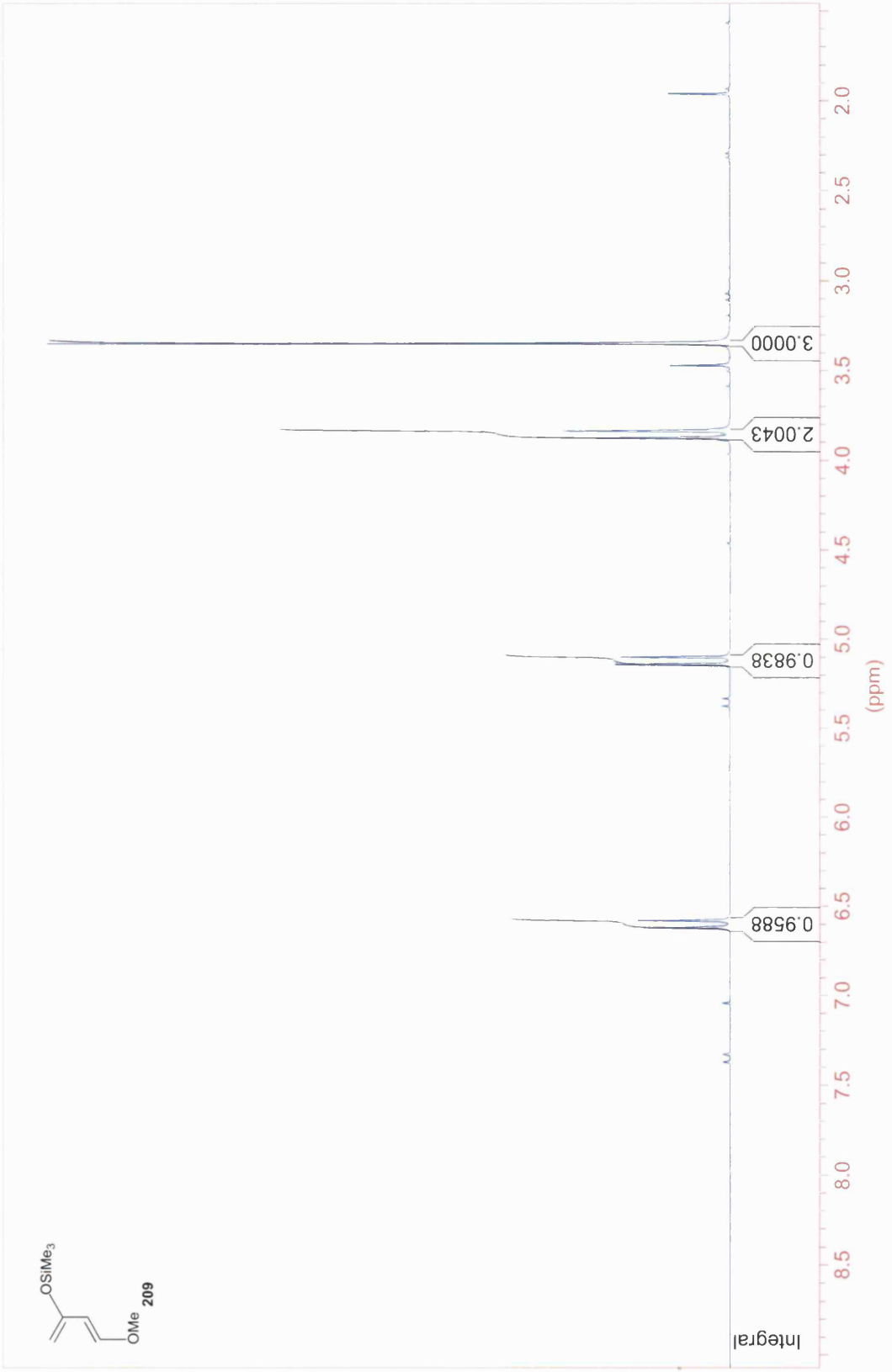
## 1.2 $^{1}$H NMR Spectrum of *N*-Benzylidene(phenyl)methanamine 218a



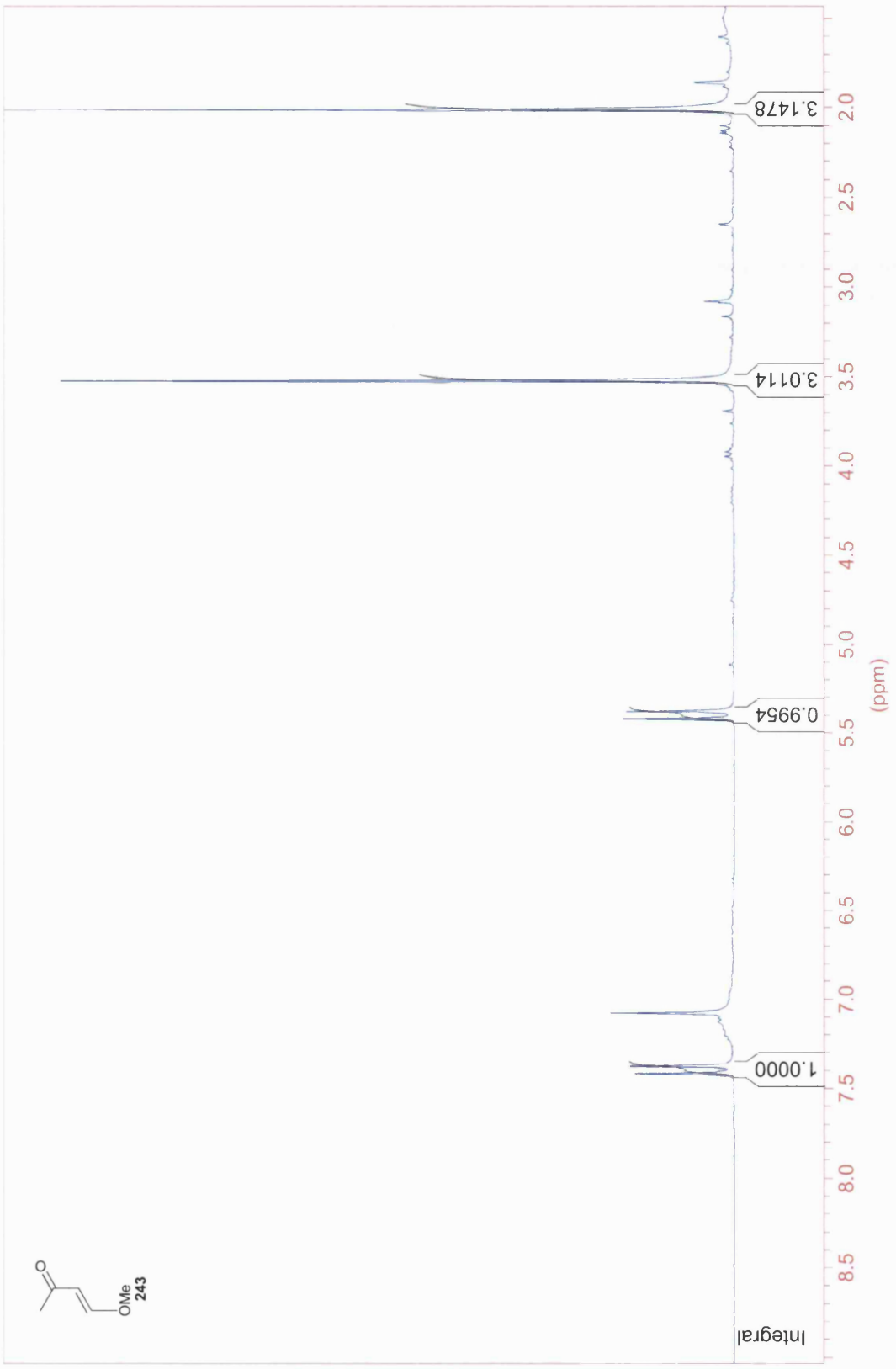
## 1.3 $^{1}$H NMR Spectrum of (*rac*)-231 and *N*-Benzylidene(phenyl) methanamine 218a



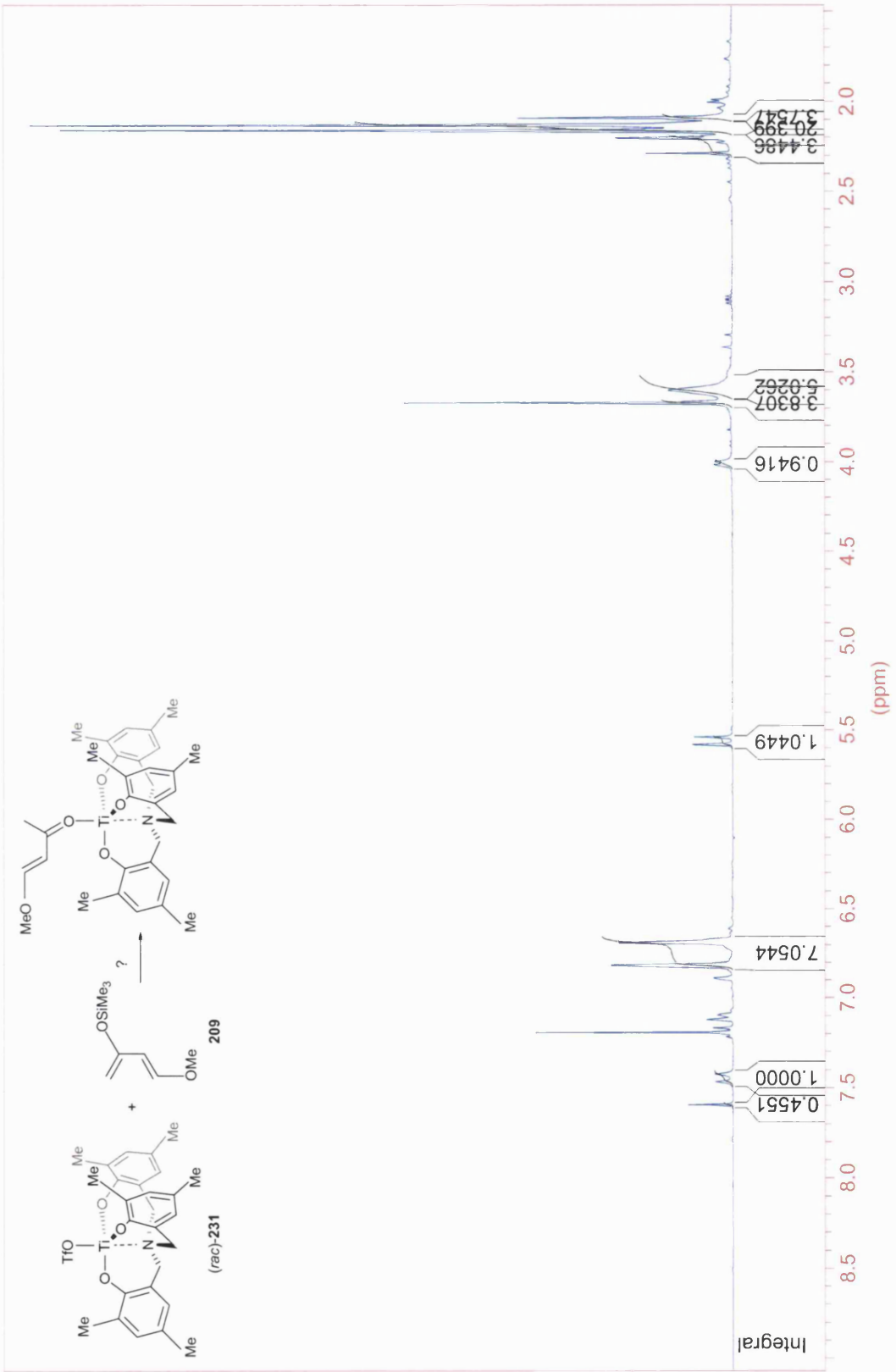
## 1.4 $^{1}$H NMR Spectrum of Danishefsky's diene 209



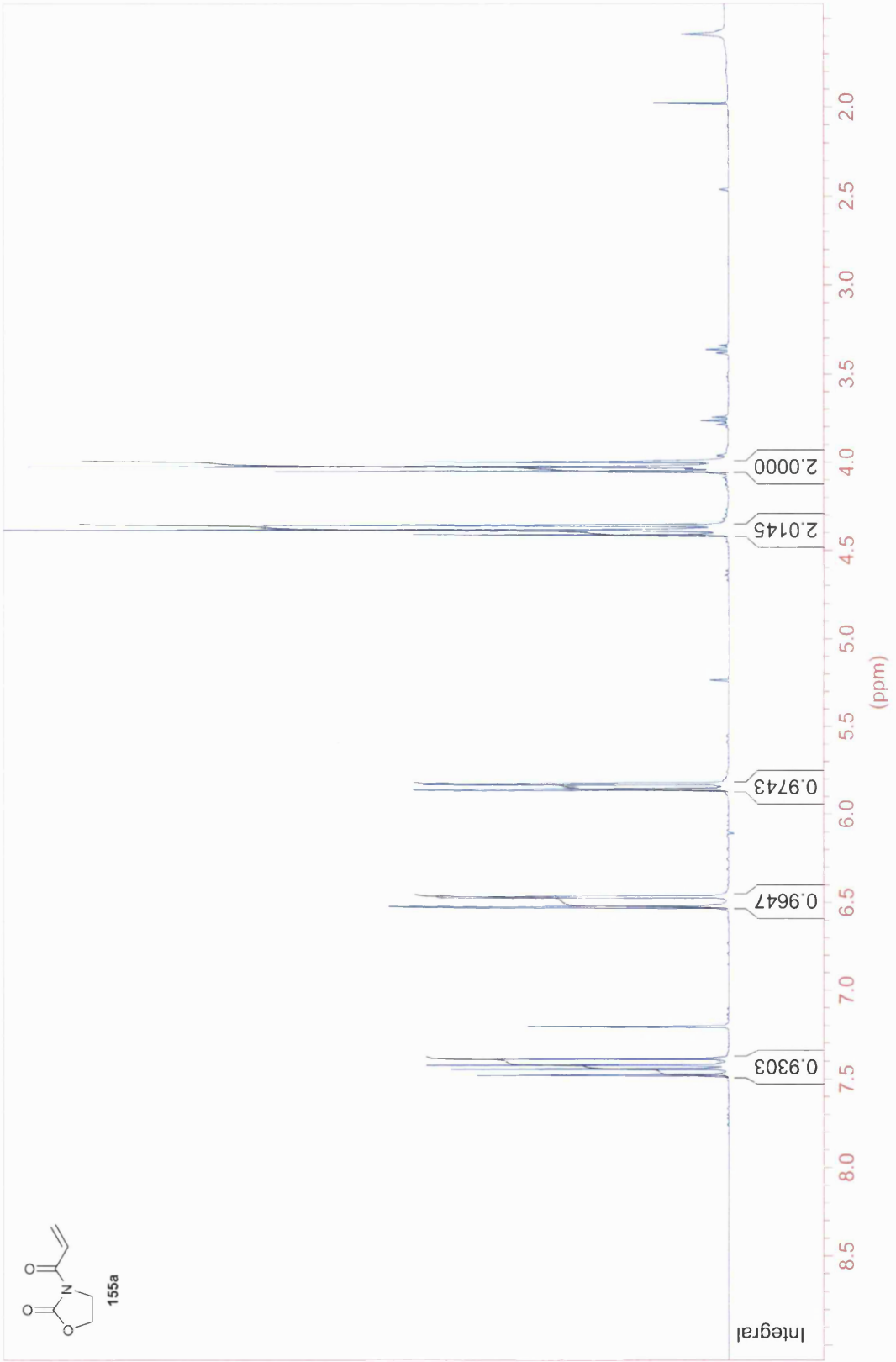
## 1.5 $^{1}$H NMR Spectrum of Methyl ketone 243



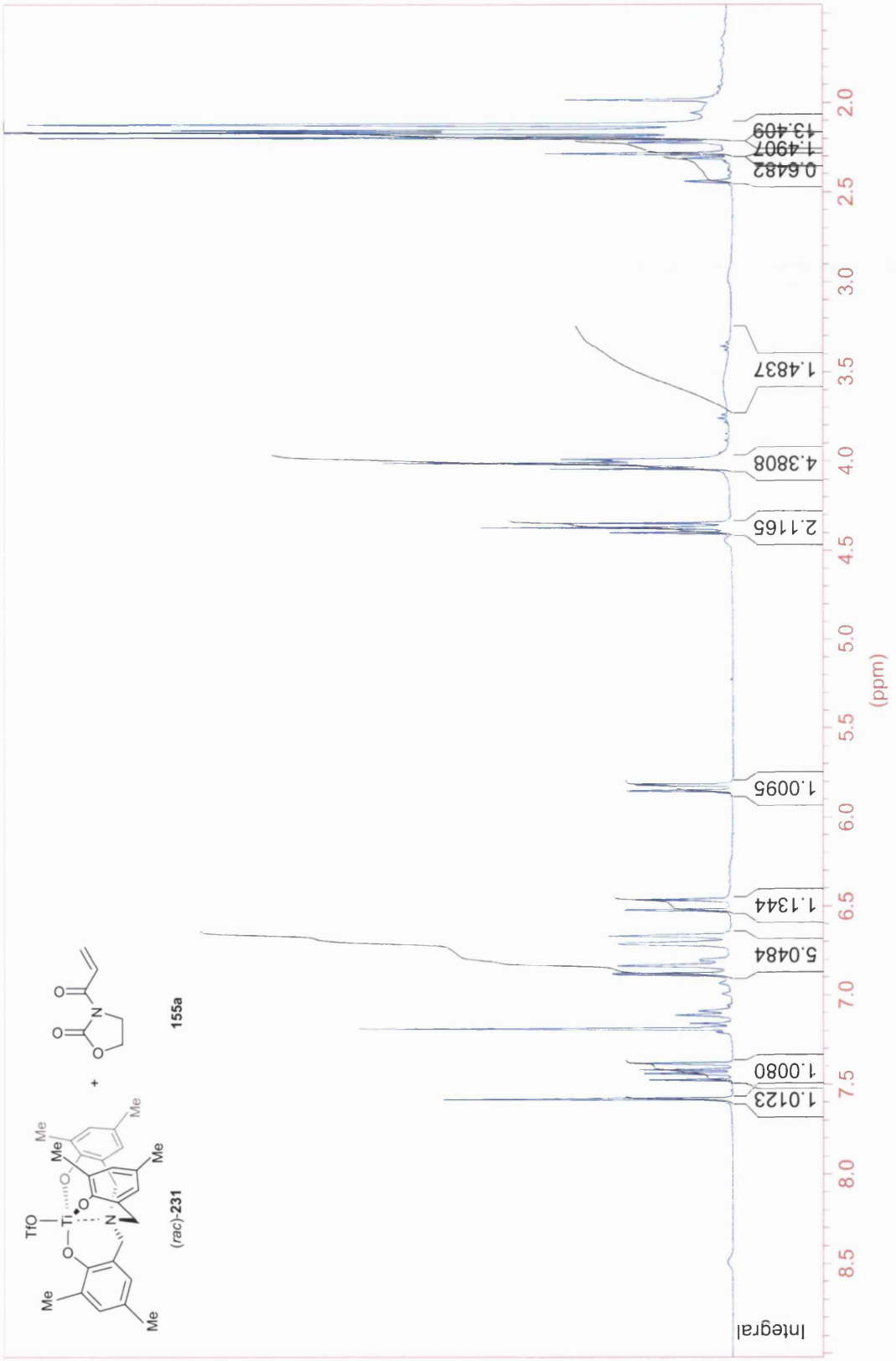
## 1.6 $^1$H NMR Spectrum of (*rac*)-231 and Danishefsky's diene 209



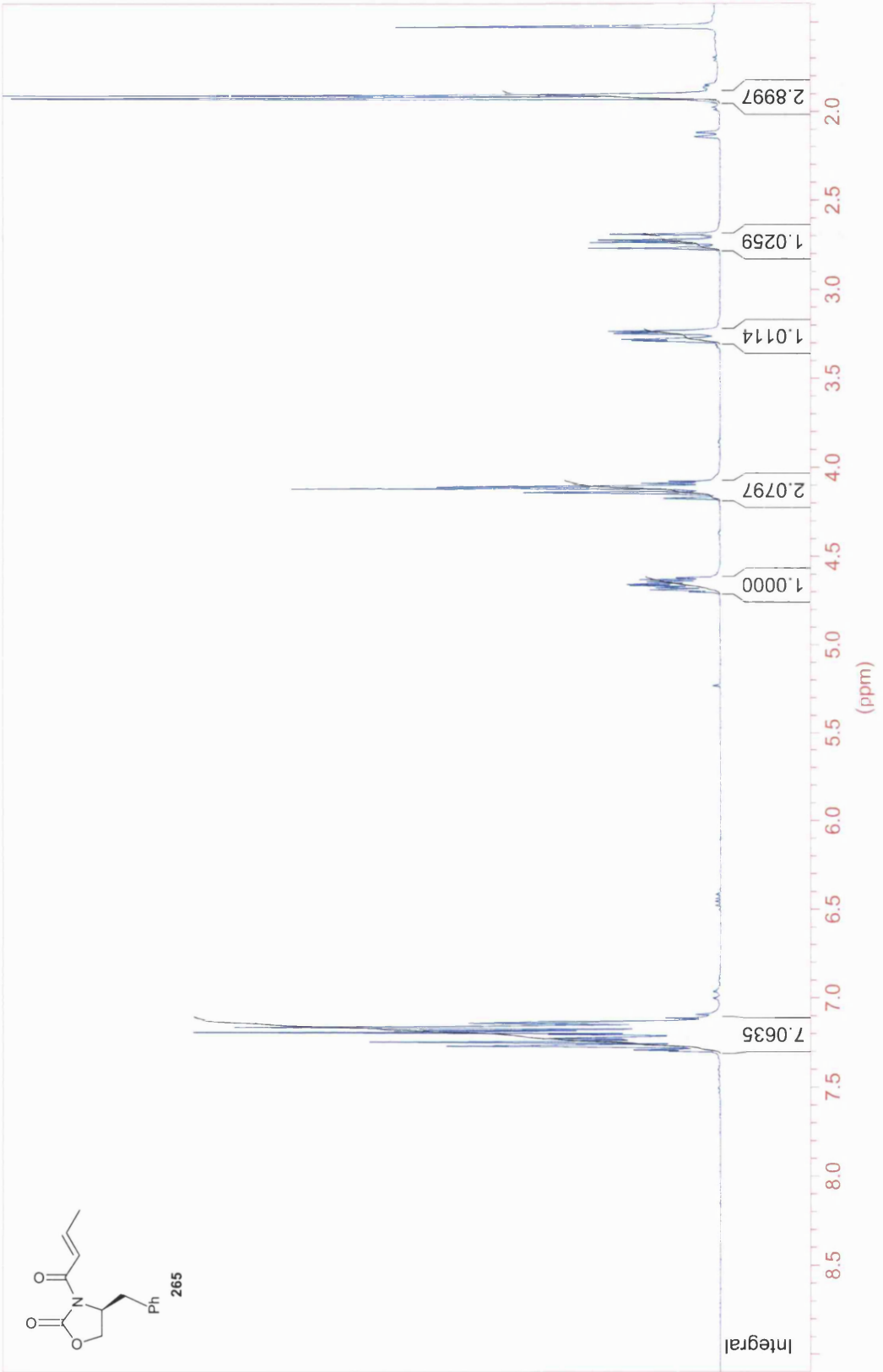
## 1.7 $^{1}$H NMR Spectrum of Oxazolidin-2-one 155a



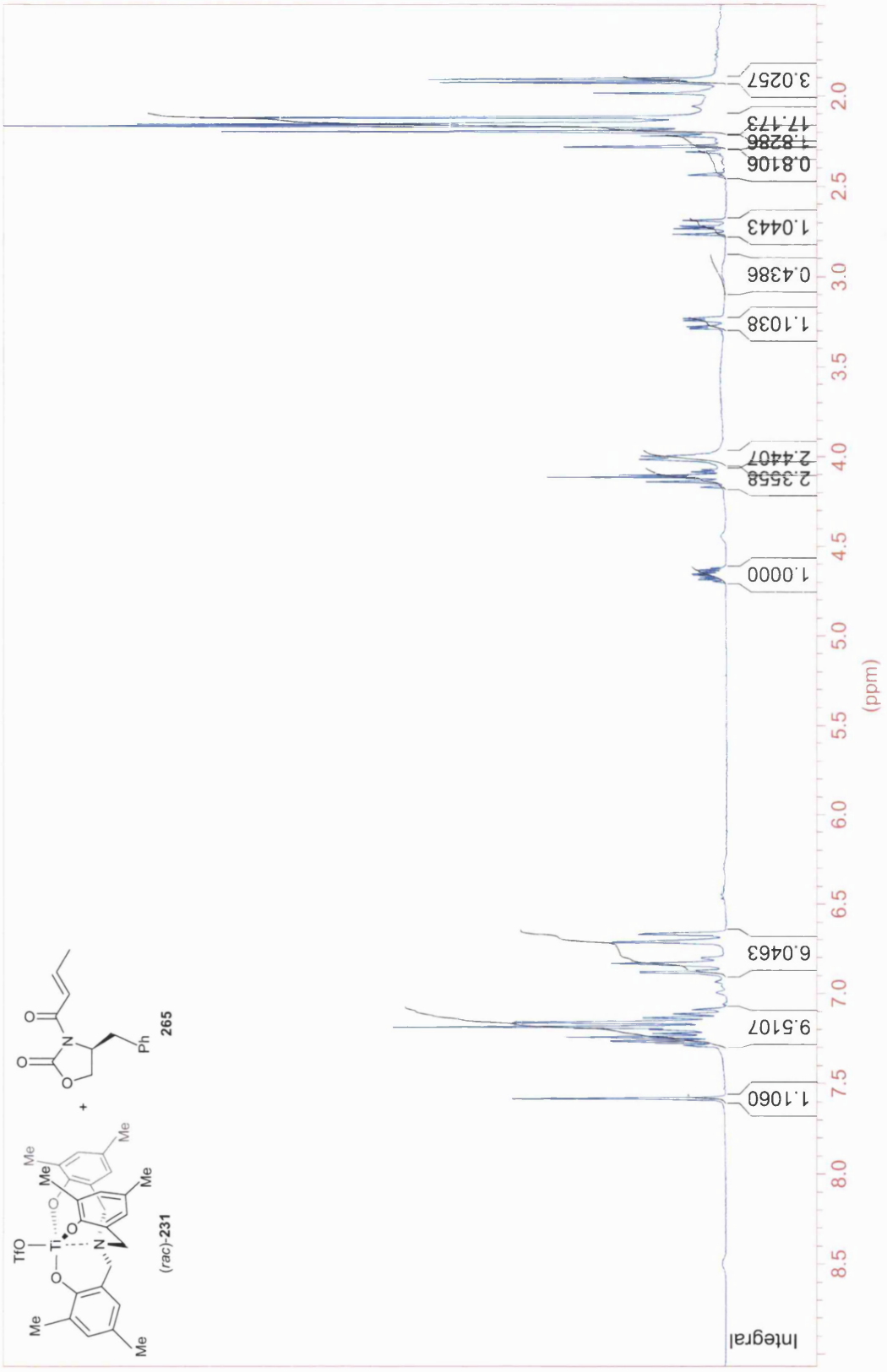
## 1.8 $^1$H NMR Spectrum of (*rac*)-231 and Oxazolidin-2-one 155a



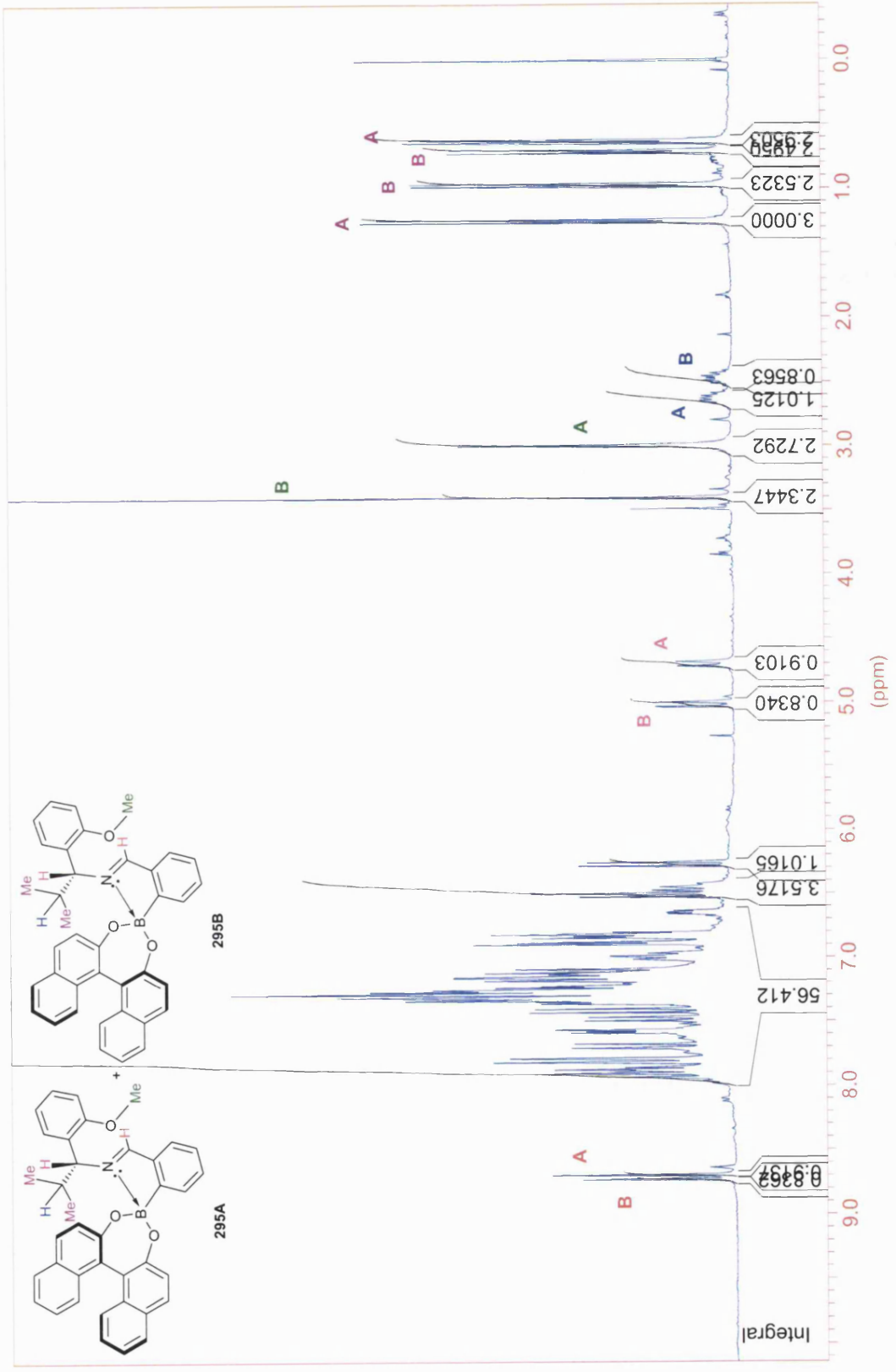
## 1.9 $^{1}$H NMR Spectrum of (*S*)-4-Benzyl-*N*-but-2-enoyloxazolidin-2-one 265



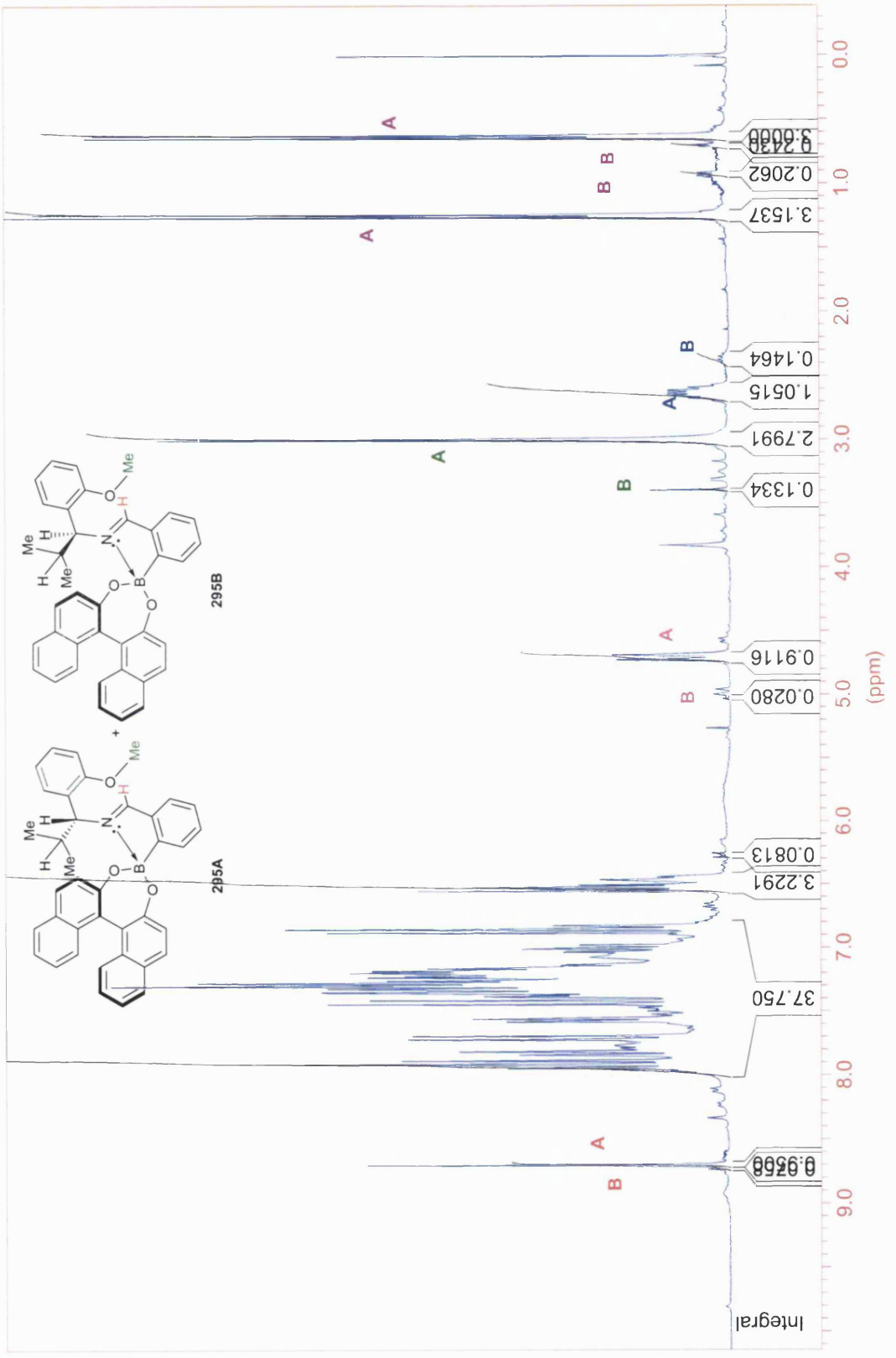
## 1.10 $^1$H NMR Spectrum of (*rac*)-231 and (*S*)-4-Benzyl-*N*-but-2-enoyloxazolidin-2-one 265



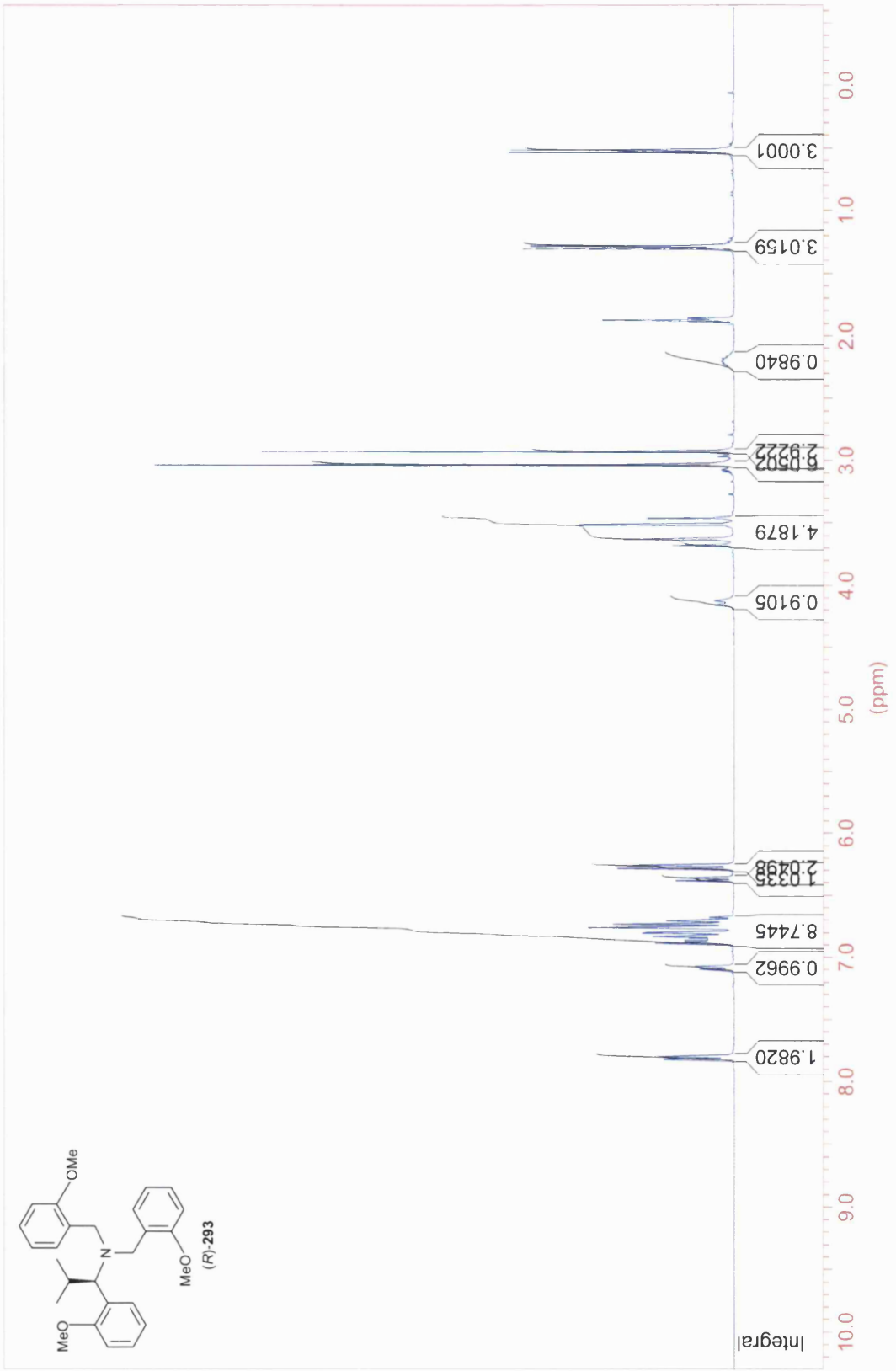
## 1.11 $^{1}$H NMR Spectrum of 295A and 295B formed with (*rac*)-BINOL



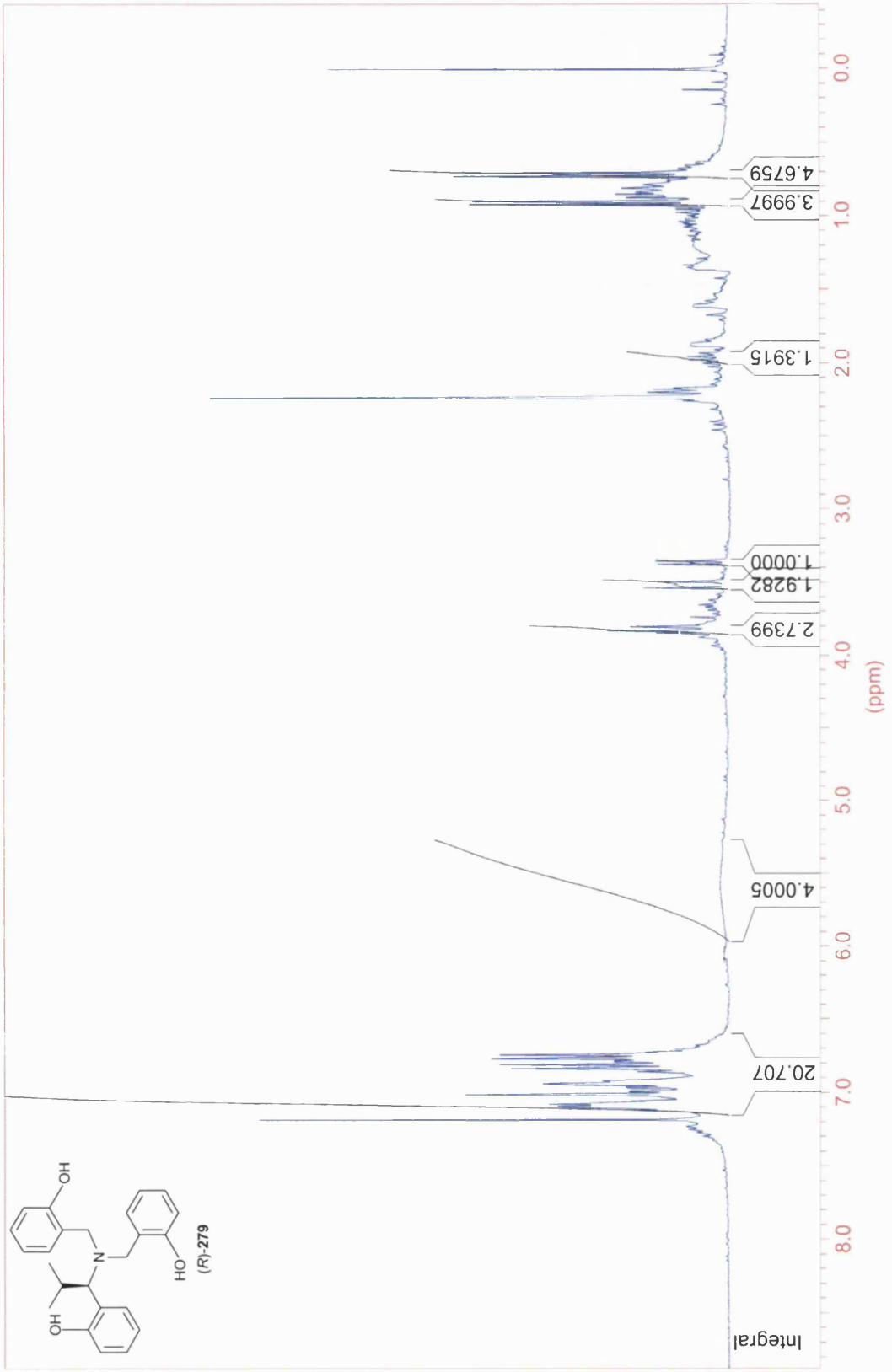
## 1.12 $^{1}$H NMR Spectrum of 295A and 295B formed with (*S*)-BINOL



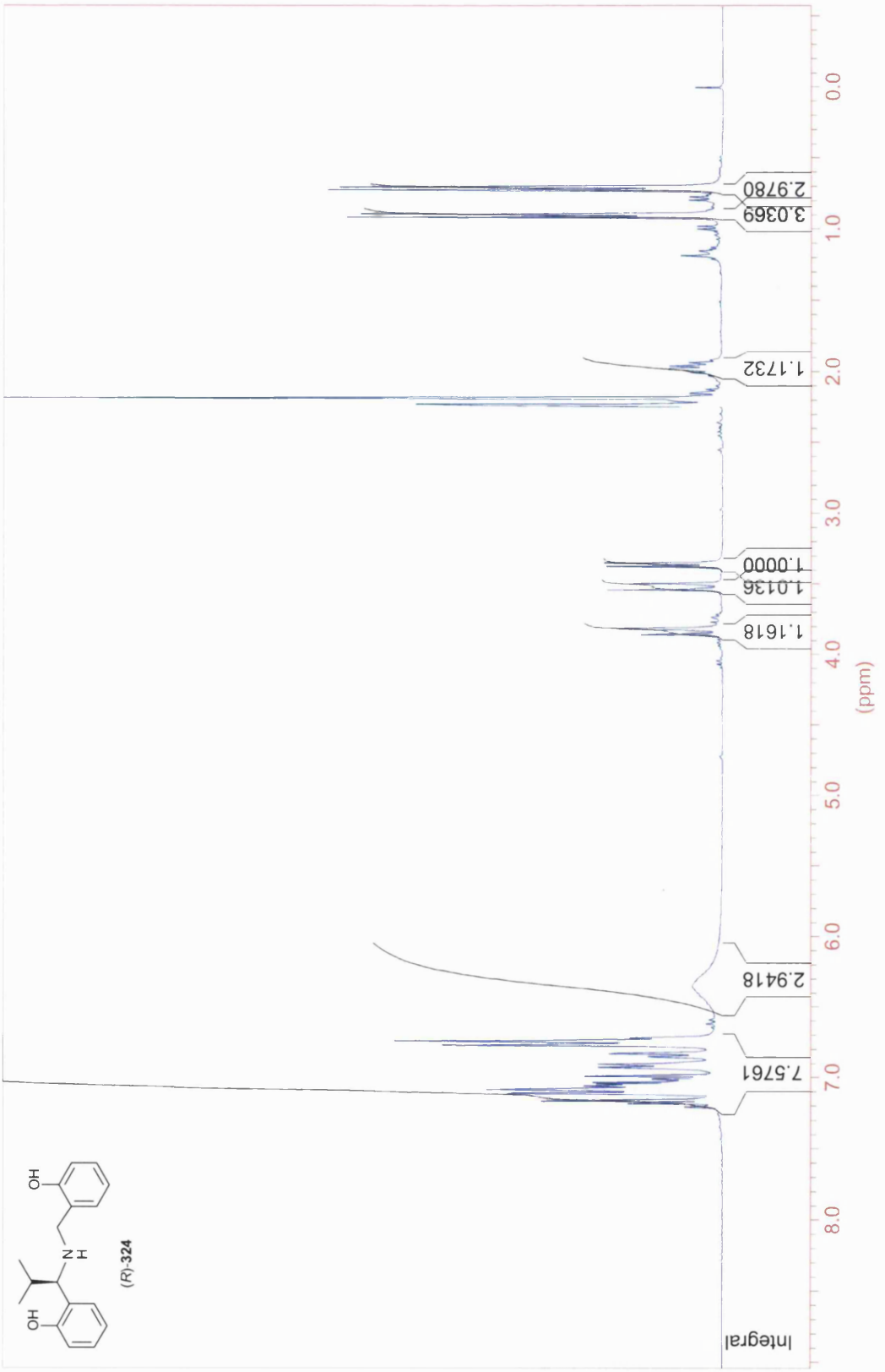
## 1.13 $^{1}$H NMR Spectrum of (*R*)-293



## 1.14 $^{1}$H NMR Spectrum of Partially Purified (*R*)-279



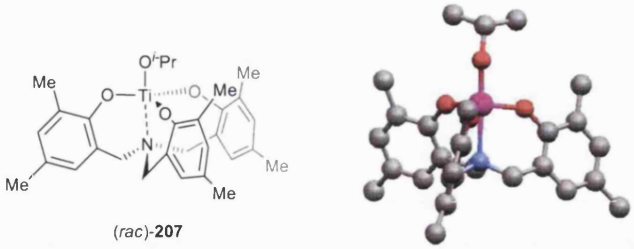
## 1.15 $^{1}$H NMR Spectrum of Partially Purified (*R*)-279



# APPENDIX 2:
# *Crystal Structure Data*

# 2 CRYSTAL STRUCTURE DATA

## 2.1 Crystal Structure Data for (*rac*)-207




(*rac*)-**207**

**Figure 1** *Compiex (rac)-**207** and its crystal structure*

**Table 1** *Crystal data and structure refinement for (rac)-**207***

| | | |
|---|---|---|
| Empirical formula | $C_{30}H_{37}NO_4Ti$ | |
| Formula weight | 523.51 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Triclinic | |
| Space group | P-1 | |
| Unit cell dimensions | a = 13.07600(10) Å | α = 82.1700(10)°. |
| | b = 14.2000(2) Å | β = 88.7580(10)°. |
| | c = 16.4720(3) Å | γ = 62.7850(10)°. |
| Volume | 2691.70(7) Å$^3$ | |
| Z | 4 | |
| Density (calculated) | 1.292 Mg/m$^3$ | |
| Absorption coefficient | 0.353 mm$^{-1}$ | |
| F(000) | 1112 | |
| Crystal size | 0.25 x 0.22 x 0.17 mm$^3$ | |
| Theta range for data collection | 3.64 to 27.51°. | |
| Index ranges | -16<=h<=16, -18<=k<=17, -21<=l<=21 | |
| Reflections collected | 52968 | |
| Independent reflections | 12285 [R(int) = 0.0556] | |
| Completeness to theta = 27.51° | 99.3 % | |
| Absorption correction | None | |
| Max. and min. transmission | 0.9424 and 0.9169 | |
| Refinement method | Full-matrix least-squares on F$^2$ | |
| Data / restraints / parameters | 12285 / 0 / 666 | |
| Goodness-of-fit on F2 | 1.024 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0500, wR2 = 0.1181 | |
| R indices (all data) | R1 = 0.0803, wR2 = 0.1306 | |
| Extinction coefficient | 0.0106(12) | |
| Largest diff. peak and hole | 0.337 and -0.602 e.Å$^{-3}$ | |

**Table 2** *Atomic coordinates (x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for (rac)-**207***

| | x | y | z | U(eq)[a] |
|---|---|---|---|---|
| Ti(1) | 8958(1) | 1805(1) | 2615(1) | 33(1) |
| Ti(2) | 4356(1) | 1641(1) | 7638(1) | 35(1) |
| O(1) | 9645(1) | 2344(1) | 1807(1) | 40(1) |
| O(2) | 7496(1) | 2729(1) | 2885(1) | 38(1) |
| O(3) | 9938(1) | 668(1) | 3370(1) | 37(1) |
| O(4) | 8578(2) | 1065(1) | 2006(1) | 45(1) |
| O(5) | 4839(1) | 2616(1) | 7858(1) | 39(1) |
| O(6) | 3218(2) | 2105(1) | 6809(1) | 43(1) |
| O(7) | 4449(1) | 543(1) | 8424(1) | 38(1) |
| O(8) | 5539(2) | 864(1) | 7066(1) | 45(1) |
| N(1) | 9463(2) | 2759(1) | 3407(1) | 30(1) |
| N(2) | 2817(2) | 2635(1) | 8372(1) | 32(1) |
| C(1) | 10637(2) | 2618(2) | 3220(1) | 34(1) |
| C(2) | 8642(2) | 3919(2) | 3243(1) | 33(1) |
| C(3) | 9438(2) | 2356(2) | 4289(1) | 33(1) |
| C(5) | 2484(2) | 3798(2) | 8175(1) | 35(1) |
| C(6) | 1812(2) | 2467(2) | 8180(1) | 36(1) |
| C(7) | 3154(2) | 2297(2) | 9266(1) | 34(1) |
| C(11) | 10242(2) | 2919(2) | 1695(1) | 37(1) |
| C(12) | 10351(2) | 3336(2) | 896(2) | 41(1) |
| C(13) | 10994(2) | 3899(2) | 794(2) | 45(1) |
| C(14) | 11532(2) | 4049(2) | 1445(2) | 44(1) |
| C(15) | 11369(2) | 3653(2) | 2228(2) | 40(1) |
| C(16) | 10731(2) | 3094(2) | 2366(1) | 35(1) |
| C(17) | 9838(2) | 3119(2) | 183(2) | 51(1) |
| C(18) | 12291(3) | 4595(2) | 1311(2) | 59(1) |
| C(21) | 6893(2) | 3616(2) | 3246(1) | 35(1) |
| C(22) | 5725(2) | 3941(2) | 3384(2) | 41(1) |
| C(23) | 5119(2) | 4865(2) | 3738(2) | 45(1) |
| C(24) | 5621(2) | 5474(2) | 3963(2) | 42(1) |
| C(25) | 6788(2) | 5122(2) | 3828(1) | 38(1) |
| C(26) | 7427(2) | 4205(2) | 3467(1) | 34(1) |
| C(27) | 5146(2) | 3315(2) | 3132(2) | 54(1) |
| C(28) | 4915(2) | 6498(2) | 4312(2) | 55(1) |
| C(31) | 10572(2) | 441(2) | 4073(1) | 35(1) |
| C(32) | 11442(2) | -608(2) | 4313(2) | 38(1) |
| C(33) | 12101(2) | -811(2) | 5028(2) | 42(1) |
| C(34) | 11937(2) | -24(2) | 5505(2) | 40(1) |
| C(35) | 11069(2) | 1001(2) | 5251(1) | 37(1) |
| C(36) | 10387(2) | 1240(2) | 4546(1) | 33(1) |

[a] U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

**Table 2** *(cont)*

| | x | y | z | U(eq)[a] |
|---|---|---|---|---|
| C(37) | 11646(2) | -1466(2) | 3794(2) | 49(1) |
| C(38) | 12693(2) | -261(2) | 6264(2) | 50(1) |
| C(41) | 8660(3) | 315(3) | 1494(2) | 63(1) |
| C(42) | 8882(3) | 683(4) | 646(2) | 91(1) |
| C(43) | 9609(3) | -783(3) | 1850(3) | 81(1) |
| C(51) | 4523(2) | 3517(2) | 8210(1) | 36(1) |
| C(52) | 5350(2) | 3845(2) | 8357(2) | 41(1) |
| C(53) | 4997(2) | 4775(2) | 8716(2) | 47(1) |
| C(54) | 3873(2) | 5373(2) | 8932(2) | 43(1) |
| C(55) | 3074(2) | 5015(2) | 8772(1) | 39(1) |
| C(56) | 3384(2) | 4099(2) | 8412(1) | 34(1) |
| C(57) | 6566(2) | 3242(2) | 8109(2) | 55(1) |
| C(58) | 3522(3) | 6389(2) | 9293(2) | 55(1) |
| C(61) | 2071(2) | 2700(2) | 6665(2) | 41(1) |
| C(62) | 1638(3) | 3101(2) | 5854(2) | 48(1) |
| C(63) | 449(3) | 3703(2) | 5723(2) | 56(1) |
| C(64) | -319(2) | 3893(2) | 6351(2) | 53(1) |
| C(65) | 148(2) | 3503(2) | 7149(2) | 45(1) |
| C(66) | 1330(2) | 2914(2) | 7314(2) | 38(1) |
| C(67) | 2444(3) | 2826(3) | 5161(2) | 64(1) |
| C(68) | -1608(3) | 4461(3) | 6181(2) | 76(1) |
| C(71) | 3991(2) | 347(2) | 9136(1) | 35(1) |
| C(72) | 4183(2) | -701(2) | 9425(2) | 39(1) |
| C(73) | 3683(2) | -863(2) | 10154(2) | 43(1) |
| C(74) | 3010(2) | -40(2) | 10591(2) | 42(1) |
| C(75) | 2840(2) | 981(2) | 10289(1) | 39(1) |
| C(76) | 3323(2) | 1185(2) | 9569(1) | 35(1) |
| C(77) | 4895(2) | -1596(2) | 8950(2) | 48(1) |
| C(78) | 2444(2) | -234(2) | 11361(2) | 52(1) |
| C(81) | 6183(2) | 42(2) | 6587(2) | 53(1) |
| C(82) | 6254(3) | -1003(2) | 6994(2) | 70(1) |
| C(83) | 5623(3) | 367(3) | 5748(2) | 70(1) |

[a] U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

**Table 3** *Bond lengths for (rac)-**207***

| Bond | Length /Å | Bond | Length /Å |
|---|---|---|---|
| Ti(1)-O(4) | 1.7733(16) | C(7)-H(7B) | 0.9900 |
| Ti(1)-O(2) | 1.8441(16) | C(11)-C(16) | 1.394(3) |
| Ti(1)-O(3) | 1.8500(16) | C(11)-C(12) | 1.400(3) |
| Ti(1)-O(1) | 1.8617(16) | C(12)-C(13) | 1.394(4) |
| Ti(1)-N(1) | 2.3037(18) | C(12)-C(17) | 1.500(4) |
| Ti(2)-O(8) | 1.7767(17) | C(13)-C(14) | 1.386(4) |
| Ti(2)-O(5) | 1.8414(16) | C(13)-H(13) | 0.9500 |
| Ti(2)-O(7) | 1.8461(16) | C(14)-C(15) | 1.387(3) |
| Ti(2)-O(6) | 1.8605(17) | C(14)-C(18) | 1.512(3) |
| Ti(2)-N(2) | 2.2952(19) | C(15)-C(16) | 1.388(3) |
| O(1)-C(11) | 1.359(3) | C(15)-H(15) | 0.9500 |
| O(2)-C(21) | 1.355(3) | C(17)-H(17A) | 0.9800 |
| O(3)-C(31) | 1.352(3) | C(17)-H(17B) | 0.9800 |
| O(4)-C(41) | 1.412(3) | C(17)-H(17C) | 0.9800 |
| O(5)-C(51) | 1.362(3) | C(18)-H(18A) | 0.9800 |
| O(6)-C(61) | 1.349(3) | C(18)-H(18B) | 0.9800 |
| O(7)-C(71) | 1.358(3) | C(18)-H(18C) | 0.9800 |
| O(8)-C(81) | 1.420(3) | C(21)-C(26) | 1.395(3) |
| N(1)-C(1) | 1.486(3) | C(21)-C(22) | 1.402(3) |
| N(1)-C(2) | 1.488(3) | C(22)-C(23) | 1.388(4) |
| N(1)-C(3) | 1.492(3) | C(22)-C(27) | 1.506(4) |
| N(2)-C(6) | 1.486(3) | C(23)-C(24) | 1.391(4) |
| N(2)-C(5) | 1.491(3) | C(23)-H(23) | 0.9500 |
| N(2)-C(7) | 1.495(3) | C(24)-C(25) | 1.395(3) |
| C(1)-C(16) | 1.504(3) | C(24)-C(28) | 1.507(4) |
| C(1)-H(1A) | 0.9900 | C(25)-C(26) | 1.394(3) |
| C(1)-H(1B) | 0.9900 | C(25)-H(25) | 0.9500 |
| C(2)-C(26) | 1.501(3) | C(27)-H(27A) | 0.9800 |
| C(2)-H(2A) | 0.9900 | C(27)-H(27B) | 0.9800 |
| C(2)-H(2B) | 0.9900 | C(27)-H(27C) | 0.9800 |
| C(3)-C(36) | 1.508(3) | C(28)-H(28A) | 0.9800 |
| C(3)-H(3A) | 0.9900 | C(28)-H(28B) | 0.9800 |
| C(3)-H(3B) | 0.9900 | C(28)-H(28C) | 0.9800 |
| C(5)-C(56) | 1.499(3) | C(31)-C(36) | 1.391(3) |
| C(5)-H(5A) | 0.9900 | C(31)-C(32) | 1.406(3) |
| C(5)-H(5B) | 0.9900 | C(32)-C(33) | 1.391(3) |
| C(6)-C(66) | 1.504(3) | C(32)-C(37) | 1.504(3) |
| C(6)-H(6A) | 0.9900 | C(33)-C(34) | 1.387(4) |
| C(6)-H(6B) | 0.9900 | C(33)-H(33) | 0.9500 |
| C(7)-C(76) | 1.504(3) | C(34)-C(35) | 1.387(3) |
| C(7)-H(7A) | 0.9900 | C(34)-C(38) | 1.513(3) |

**Table 3** *(cont)*

| Bond | Length /Å | Bond | Length /Å |
|---|---|---|---|
| C(35)-C(36) | 1.386(3) | C(63)-C(64) | 1.391(4) |
| C(35)-H(35) | 0.9500 | C(63)-H(63) | 0.9500 |
| C(37)-H(37A) | 0.9800 | C(64)-C(65) | 1.390(4) |
| C(37)-H(37B) | 0.9800 | C(64)-C(68) | 1.512(4) |
| C(37)-H(37C) | 0.9800 | C(65)-C(66) | 1.391(3) |
| C(38)-H(38A) | 0.9800 | C(65)-H(65) | 0.9500 |
| C(38)-H(38B) | 0.9800 | C(67)-H(67A) | 0.9800 |
| C(38)-H(38C) | 0.9800 | C(67)-H(67B) | 0.9800 |
| C(41)-C(42) | 1.493(5) | C(67)-H(67C) | 0.9800 |
| C(41)-C(43) | 1.525(5) | C(68)-H(68A) | 0.9800 |
| C(41)-H(41) | 1.0000 | C(68)-H(68B) | 0.9800 |
| C(42)-H(42A) | 0.9800 | C(68)-H(68C) | 0.9800 |
| C(42)-H(42B) | 0.9800 | C(71)-C(76) | 1.392(3) |
| C(42)-H(42C) | 0.9800 | C(71)-C(72) | 1.406(3) |
| C(43)-H(43A) | 0.9800 | C(72)-C(73) | 1.395(3) |
| C(43)-H(43B) | 0.9800 | C(72)-C(77) | 1.501(4) |
| C(43)-H(43C) | 0.9800 | C(73)-C(74) | 1.386(4) |
| C(51)-C(56) | 1.393(3) | C(73)-H(73) | 0.9500 |
| C(51)-C(52) | 1.395(3) | C(74)-C(75) | 1.384(3) |
| C(52)-C(53) | 1.396(4) | C(74)-C(78) | 1.510(3) |
| C(52)-C(57) | 1.501(4) | C(75)-C(76) | 1.389(3) |
| C(53)-C(54) | 1.389(4) | C(75)-H(75) | 0.9500 |
| C(53)-H(53) | 0.9500 | C(77)-H(77A) | 0.9800 |
| C(54)-C(55) | 1.398(3) | C(77)-H(77B) | 0.9800 |
| C(54)-C(58) | 1.503(4) | C(77)-H(77C) | 0.9800 |
| C(55)-C(56) | 1.387(3) | C(78)-H(78A) | 0.9800 |
| C(55)-H(55) | 0.9500 | C(78)-H(78B) | 0.9800 |
| C(57)-H(57A) | 0.9800 | C(78)-H(78C) | 0.9800 |
| C(57)-H(57B) | 0.9800 | C(81)-C(83) | 1.490(4) |
| C(57)-H(57C) | 0.9800 | C(81)-C(82) | 1.505(4) |
| C(58)-H(58A) | 0.9800 | C(81)-H(81) | 1.0000 |
| C(58)-H(58B) | 0.9800 | C(82)-H(82A) | 0.9800 |
| C(58)-H(58C) | 0.9800 | C(82)-H(82B) | 0.9800 |
| C(61)-C(66) | 1.396(4) | C(82)-H(82C) | 0.9800 |
| C(61)-C(62) | 1.400(3) | C(83)-H(83A) | 0.9800 |
| C(62)-C(63) | 1.393(4) | C(83)-H(83B) | 0.9800 |
| C(62)-C(67) | 1.503(4) | C(83)-H(83C) | 0.9800 |

**Table 4** *Bond angles for (rac)-**207***

| Bond | Angle /° | Bond | Angle /° |
|---|---|---|---|
| O(4)-Ti(1)-O(2) | 98.09(8) | N(1)-C(1)-H(1A) | 108.7 |
| O(4)-Ti(1)-O(3) | 97.64(8) | C(16)-C(1)-H(1A) | 108.7 |
| O(2)-Ti(1)-O(3) | 120.84(7) | N(1)-C(1)-H(1B) | 108.7 |
| O(4)-Ti(1)-O(1) | 97.62(8) | C(16)-C(1)-H(1B) | 108.7 |
| O(2)-Ti(1)-O(1) | 117.07(7) | H(1A)-C(1)-H(1B) | 107.6 |
| O(3)-Ti(1)-O(1) | 116.67(7) | N(1)-C(2)-C(26) | 115.10(17) |
| O(4)-Ti(1)-N(1) | 179.68(8) | N(1)-C(2)-H(2A) | 108.5 |
| O(2)-Ti(1)-N(1) | 82.23(7) | C(26)-C(2)-H(2A) | 108.5 |
| O(3)-Ti(1)-N(1) | 82.13(6) | N(1)-C(2)-H(2B) | 108.5 |
| O(1)-Ti(1)-N(1) | 82.30(7) | C(26)-C(2)-H(2B) | 108.5 |
| O(8)-Ti(2)-O(5) | 98.17(8) | H(2A)-C(2)-H(2B) | 107.5 |
| O(8)-Ti(2)-O(7) | 97.56(8) | N(1)-C(3)-C(36) | 112.82(18) |
| O(5)-Ti(2)-O(7) | 121.98(7) | N(1)-C(3)-H(3A) | 109.0 |
| O(8)-Ti(2)-O(6) | 97.32(8) | C(36)-C(3)-H(3A) | 109.0 |
| O(5)-Ti(2)-O(6) | 116.54(8) | N(1)-C(3)-H(3B) | 109.0 |
| O(7)-Ti(2)-O(6) | 116.18(7) | C(36)-C(3)-H(3B) | 109.0 |
| O(8)-Ti(2)-N(2) | 179.37(8) | H(3A)-C(3)-H(3B) | 107.8 |
| O(5)-Ti(2)-N(2) | 82.44(7) | N(2)-C(5)-C(56) | 114.51(18) |
| O(7)-Ti(2)-N(2) | 82.21(7) | N(2)-C(5)-H(5A) | 108.6 |
| O(6)-Ti(2)-N(2) | 82.26(7) | C(56)-C(5)-H(5A) | 108.6 |
| C(11)-O(1)-Ti(1) | 141.70(15) | N(2)-C(5)-H(5B) | 108.6 |
| C(21)-O(2)-Ti(1) | 143.19(15) | C(56)-C(5)-H(5B) | 108.6 |
| C(31)-O(3)-Ti(1) | 141.87(14) | H(5A)-C(5)-H(5B) | 107.6 |
| C(41)-O(4)-Ti(1) | 161.56(18) | N(2)-C(6)-C(66) | 113.17(18) |
| C(51)-O(5)-Ti(2) | 143.20(15) | N(2)-C(6)-H(6A) | 108.9 |
| C(61)-O(6)-Ti(2) | 141.30(16) | C(66)-C(6)-H(6A) | 108.9 |
| C(71)-O(7)-Ti(2) | 142.17(15) | N(2)-C(6)-H(6B) | 108.9 |
| C(81)-O(8)-Ti(2) | 156.08(17) | C(66)-C(6)-H(6B) | 108.9 |
| C(1)-N(1)-C(2) | 108.52(16) | H(6A)-C(6)-H(6B) | 107.8 |
| C(1)-N(1)-C(3) | 109.73(16) | N(2)-C(7)-C(76) | 113.20(19) |
| C(2)-N(1)-C(3) | 109.16(17) | N(2)-C(7)-H(7A) | 108.9 |
| C(1)-N(1)-Ti(1) | 110.16(13) | C(76)-C(7)-H(7A) | 108.9 |
| C(2)-N(1)-Ti(1) | 110.73(13) | N(2)-C(7)-H(7B) | 108.9 |
| C(3)-N(1)-Ti(1) | 108.53(13) | C(76)-C(7)-H(7B) | 108.9 |
| C(6)-N(2)-C(5) | 108.75(16) | H(7A)-C(7)-H(7B) | 107.8 |
| C(6)-N(2)-C(7) | 110.04(17) | O(1)-C(11)-C(16) | 120.4(2) |
| C(5)-N(2)-C(7) | 108.28(17) | O(1)-C(11)-C(12) | 118.9(2) |
| C(6)-N(2)-Ti(2) | 110.16(14) | C(16)-C(11)-C(12) | 120.7(2) |
| C(5)-N(2)-Ti(2) | 111.01(13) | C(13)-C(12)-C(11) | 117.9(2) |
| C(7)-N(2)-Ti(2) | 108.57(13) | C(13)-C(12)-C(17) | 122.3(2) |
| N(1)-C(1)-C(16) | 114.10(18) | C(11)-C(12)-C(17) | 119.7(2) |

**Table 4** *(cont)*

| Bond | Angle /° | Bond | Angle /° |
|---|---|---|---|
| C(14)-C(13)-C(12) | 122.8(2) | C(22)-C(27)-H(27B) | 109.5 |
| C(14)-C(13)-H(13) | 118.6 | H(27A)-C(27)-H(27B) | 109.5 |
| C(12)-C(13)-H(13) | 118.6 | C(22)-C(27)-H(27C) | 109.5 |
| C(13)-C(14)-C(15) | 117.3(2) | H(27A)-C(27)-H(27C) | 109.5 |
| C(13)-C(14)-C(18) | 121.6(2) | H(27B)-C(27)-H(27C) | 109.5 |
| C(15)-C(14)-C(18) | 121.0(2) | C(24)-C(28)-H(28A) | 109.5 |
| C(14)-C(15)-C(16) | 122.2(2) | C(24)-C(28)-H(28B) | 109.5 |
| C(14)-C(15)-H(15) | 118.9 | H(28A)-C(28)-H(28B) | 109.5 |
| C(16)-C(15)-H(15) | 118.9 | C(24)-C(28)-H(28C) | 109.5 |
| C(15)-C(16)-C(11) | 118.9(2) | H(28A)-C(28)-H(28C) | 109.5 |
| C(15)-C(16)-C(1) | 120.6(2) | H(28B)-C(28)-H(28C) | 109.5 |
| C(11)-C(16)-C(1) | 120.4(2) | O(3)-C(31)-C(36) | 120.45(19) |
| C(12)-C(17)-H(17A) | 109.5 | O(3)-C(31)-C(32) | 119.4(2) |
| C(12)-C(17)-H(17B) | 109.5 | C(36)-C(31)-C(32) | 120.1(2) |
| H(17A)-C(17)-H(17B) | 109.5 | C(33)-C(32)-C(31) | 118.0(2) |
| C(12)-C(17)-H(17C) | 109.5 | C(33)-C(32)-C(37) | 122.1(2) |
| H(17A)-C(17)-H(17C) | 109.5 | C(31)-C(32)-C(37) | 119.9(2) |
| H(17B)-C(17)-H(17C) | 109.5 | C(34)-C(33)-C(32) | 122.8(2) |
| C(14)-C(18)-H(18A) | 109.5 | C(34)-C(33)-H(33) | 118.6 |
| C(14)-C(18)-H(18B) | 109.5 | C(32)-C(33)-H(33) | 118.6 |
| H(18A)-C(18)-H(18B) | 109.5 | C(33)-C(34)-C(35) | 117.7(2) |
| C(14)-C(18)-H(18C) | 109.5 | C(33)-C(34)-C(38) | 121.6(2) |
| H(18A)-C(18)-H(18C) | 109.5 | C(35)-C(34)-C(38) | 120.8(2) |
| H(18B)-C(18)-H(18C) | 109.5 | C(36)-C(35)-C(34) | 121.6(2) |
| O(2)-C(21)-C(26) | 120.2(2) | C(36)-C(35)-H(35) | 119.2 |
| O(2)-C(21)-C(22) | 119.2(2) | C(34)-C(35)-H(35) | 119.2 |
| C(26)-C(21)-C(22) | 120.5(2) | C(35)-C(36)-C(31) | 119.8(2) |
| C(23)-C(22)-C(21) | 118.2(2) | C(35)-C(36)-C(3) | 120.7(2) |
| C(23)-C(22)-C(27) | 121.4(2) | C(31)-C(36)-C(3) | 119.5(2) |
| C(21)-C(22)-C(27) | 120.4(2) | C(32)-C(37)-H(37A) | 109.5 |
| C(22)-C(23)-C(24) | 122.9(2) | C(32)-C(37)-H(37B) | 109.5 |
| C(22)-C(23)-H(23) | 118.6 | H(37A)-C(37)-H(37B) | 109.5 |
| C(24)-C(23)-H(23) | 118.6 | C(32)-C(37)-H(37C) | 109.5 |
| C(23)-C(24)-C(25) | 117.6(2) | H(37A)-C(37)-H(37C) | 109.5 |
| C(23)-C(24)-C(28) | 120.9(2) | H(37B)-C(37)-H(37C) | 109.5 |
| C(25)-C(24)-C(28) | 121.5(2) | C(34)-C(38)-H(38A) | 109.5 |
| C(26)-C(25)-C(24) | 121.4(2) | C(34)-C(38)-H(38B) | 109.5 |
| C(26)-C(25)-H(25) | 119.3 | H(38A)-C(38)-H(38B) | 109.5 |
| C(24)-C(25)-H(25) | 119.3 | C(34)-C(38)-H(38C) | 109.5 |
| C(25)-C(26)-C(21) | 119.4(2) | H(38A)-C(38)-H(38C) | 109.5 |
| C(25)-C(26)-C(2) | 119.9(2) | H(38B)-C(38)-H(38C) | 109.5 |
| C(21)-C(26)-C(2) | 120.4(2) | O(4)-C(41)-C(42) | 108.6(3) |

**Table 4** *(cont)*

| Bond | Angle /° | Bond | Angle /° |
|---|---|---|---|
| C(22)-C(27)-H(27A) | 109.5 | O(4)-C(41)-C(43) | 108.7(3) |
| C(42)-C(41)-C(43) | 112.7(3) | C(54)-C(58)-H(58C) | 109.5 |
| O(4)-C(41)-H(41) | 108.9 | H(58A)-C(58)-H(58C) | 109.5 |
| C(42)-C(41)-H(41) | 108.9 | H(58B)-C(58)-H(58C) | 109.5 |
| C(43)-C(41)-H(41) | 108.9 | O(6)-C(61)-C(66) | 120.6(2) |
| C(41)-C(42)-H(42A) | 109.5 | O(6)-C(61)-C(62) | 118.9(2) |
| C(41)-C(42)-H(42B) | 109.5 | C(66)-C(61)-C(62) | 120.6(2) |
| H(42A)-C(42)-H(42B) | 109.5 | C(63)-C(62)-C(61) | 117.7(3) |
| C(41)-C(42)-H(42C) | 109.5 | C(63)-C(62)-C(67) | 122.4(2) |
| H(42A)-C(42)-H(42C) | 109.5 | C(61)-C(62)-C(67) | 119.8(3) |
| H(42B)-C(42)-H(42C) | 109.5 | C(64)-C(63)-C(62) | 123.3(2) |
| C(41)-C(43)-H(43A) | 109.5 | C(64)-C(63)-H(63) | 118.3 |
| C(41)-C(43)-H(43B) | 109.5 | C(62)-C(63)-H(63) | 118.3 |
| H(43A)-C(43)-H(43B) | 109.5 | C(65)-C(64)-C(63) | 117.1(3) |
| C(41)-C(43)-H(43C) | 109.5 | C(65)-C(64)-C(68) | 120.8(3) |
| H(43A)-C(43)-H(43C) | 109.5 | C(63)-C(64)-C(68) | 122.0(3) |
| H(43B)-C(43)-H(43C) | 109.5 | C(64)-C(65)-C(66) | 121.7(3) |
| O(5)-C(51)-C(56) | 119.7(2) | C(64)-C(65)-H(65) | 119.1 |
| O(5)-C(51)-C(52) | 119.2(2) | C(66)-C(65)-H(65) | 119.1 |
| C(56)-C(51)-C(52) | 121.1(2) | C(65)-C(66)-C(61) | 119.5(2) |
| C(51)-C(52)-C(53) | 117.8(2) | C(65)-C(66)-C(6) | 120.7(2) |
| C(51)-C(52)-C(57) | 121.1(2) | C(61)-C(66)-C(6) | 119.7(2) |
| C(53)-C(52)-C(57) | 121.1(2) | C(62)-C(67)-H(67A) | 109.5 |
| C(54)-C(53)-C(52) | 122.9(2) | C(62)-C(67)-H(67B) | 109.5 |
| C(54)-C(53)-H(53) | 118.6 | H(67A)-C(67)-H(67B) | 109.5 |
| C(52)-C(53)-H(53) | 118.6 | C(62)-C(67)-H(67C) | 109.5 |
| C(53)-C(54)-C(55) | 117.3(2) | H(67A)-C(67)-H(67C) | 109.5 |
| C(53)-C(54)-C(58) | 121.1(2) | H(67B)-C(67)-H(67C) | 109.5 |
| C(55)-C(54)-C(58) | 121.5(2) | C(64)-C(68)-H(68A) | 109.5 |
| C(56)-C(55)-C(54) | 121.7(2) | C(64)-C(68)-H(68B) | 109.5 |
| C(56)-C(55)-H(55) | 119.1 | H(68A)-C(68)-H(68B) | 109.5 |
| C(54)-C(55)-H(55) | 119.1 | C(64)-C(68)-H(68C) | 109.5 |
| C(55)-C(56)-C(51) | 119.1(2) | H(68A)-C(68)-H(68C) | 109.5 |
| C(55)-C(56)-C(5) | 120.2(2) | H(68B)-C(68)-H(68C) | 109.5 |
| C(51)-C(56)-C(5) | 120.4(2) | O(7)-C(71)-C(76) | 120.0(2) |
| C(52)-C(57)-H(57A) | 109.5 | O(7)-C(71)-C(72) | 119.6(2) |
| C(52)-C(57)-H(57B) | 109.5 | C(76)-C(71)-C(72) | 120.4(2) |
| H(57A)-C(57)-H(57B) | 109.5 | C(73)-C(72)-C(71) | 117.6(2) |
| C(52)-C(57)-H(57C) | 109.5 | C(73)-C(72)-C(77) | 122.4(2) |
| H(57A)-C(57)-H(57C) | 109.5 | C(71)-C(72)-C(77) | 120.0(2) |
| H(57B)-C(57)-H(57C) | 109.5 | C(74)-C(73)-C(72) | 122.9(2) |
| C(54)-C(58)-H(58A) | 109.5 | C(74)-C(73)-H(73) | 118.5 |

**Table 4** *(cont)*

| Bond | Angle /° | Bond | Angle /° |
|---|---|---|---|
| C(54)-C(58)-H(58B) | 109.5 | C(72)-C(73)-H(73) | 118.5 |
| H(58A)-C(58)-H(58B) | 109.5 | C(75)-C(74)-C(73) | 117.8(2) |
| C(75)-C(74)-C(78) | 120.5(2) | H(78B)-C(78)-H(78C) | 109.5 |
| C(73)-C(74)-C(78) | 121.7(2) | O(8)-C(81)-C(83) | 108.2(2) |
| C(74)-C(75)-C(76) | 121.5(2) | O(8)-C(81)-C(82) | 109.9(2) |
| C(74)-C(75)-H(75) | 119.2 | C(83)-C(81)-C(82) | 112.4(3) |
| C(76)-C(75)-H(75) | 119.2 | O(8)-C(81)-H(81) | 108.8 |
| C(75)-C(76)-C(71) | 119.6(2) | C(83)-C(81)-H(81) | 108.8 |
| C(75)-C(76)-C(7) | 120.5(2) | C(82)-C(81)-H(81) | 108.8 |
| C(71)-C(76)-C(7) | 119.9(2) | C(81)-C(82)-H(82A) | 109.5 |
| C(72)-C(77)-H(77A) | 109.5 | C(81)-C(82)-H(82B) | 109.5 |
| C(72)-C(77)-H(77B) | 109.5 | H(82A)-C(82)-H(82B) | 109.5 |
| H(77A)-C(77)-H(77B) | 109.5 | C(81)-C(82)-H(82C) | 109.5 |
| C(72)-C(77)-H(77C) | 109.5 | H(82A)-C(82)-H(82C) | 109.5 |
| H(77A)-C(77)-H(77C) | 109.5 | H(82B)-C(82)-H(82C) | 109.5 |
| H(77B)-C(77)-H(77C) | 109.5 | C(81)-C(83)-H(83A) | 109.5 |
| C(74)-C(78)-H(78A) | 109.5 | C(81)-C(83)-H(83B) | 109.5 |
| C(74)-C(78)-H(78B) | 109.5 | H(83A)-C(83)-H(83B) | 109.5 |
| H(78A)-C(78)-H(78B) | 109.5 | C(81)-C(83)-H(83C) | 109.5 |
| C(74)-C(78)-H(78C) | 109.5 | H(83A)-C(83)-H(83C) | 109.5 |
| H(78A)-C(78)-H(78C) | 109.5 | H(83B)-C(83)-H(83C) | 109.5 |

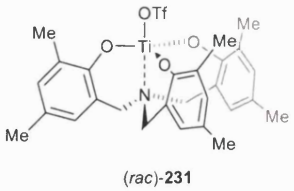
**Table 5** *Anisotropic displacement parameters ($Å^2$ × 103) for (R)-**207**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$*

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| Ti(1) | 34(1) | 28(1) | 38(1) | -4(1) | -1(1) | -14(1) |
| Ti(2) | 37(1) | 30(1) | 37(1) | -3(1) | 2(1) | -16(1) |
| O(1) | 44(1) | 43(1) | 37(1) | -7(1) | 2(1) | -23(1) |
| O(2) | 34(1) | 33(1) | 46(1) | -5(1) | -1(1) | -14(1) |
| O(3) | 40(1) | 27(1) | 42(1) | -4(1) | -1(1) | -14(1) |
| O(4) | 48(1) | 41(1) | 49(1) | -12(1) | -2(1) | -22(1) |
| O(5) | 39(1) | 32(1) | 47(1) | -4(1) | 3(1) | -18(1) |
| O(6) | 46(1) | 48(1) | 39(1) | -7(1) | 0(1) | -24(1) |
| O(7) | 39(1) | 29(1) | 43(1) | -3(1) | 3(1) | -14(1) |
| O(8) | 46(1) | 40(1) | 49(1) | -11(1) | 12(1) | -19(1) |
| N(1) | 30(1) | 24(1) | 33(1) | 0(1) | -2(1) | -10(1) |
| N(2) | 34(1) | 26(1) | 34(1) | 2(1) | -3(1) | -14(1) |
| C(1) | 33(1) | 30(1) | 39(1) | -1(1) | -2(1) | -14(1) |
| C(2) | 36(1) | 23(1) | 37(1) | -1(1) | -2(1) | -12(1) |
| C(3) | 37(1) | 25(1) | 33(1) | -1(1) | -1(1) | -12(1) |
| C(5) | 38(1) | 24(1) | 39(1) | 1(1) | -4(1) | -13(1) |
| C(6) | 35(1) | 30(1) | 41(1) | -1(1) | -2(1) | -15(1) |
| C(7) | 37(1) | 28(1) | 34(1) | 0(1) | 0(1) | -13(1) |
| C(11) | 33(1) | 35(1) | 41(1) | -4(1) | 5(1) | -14(1) |
| C(12) | 37(1) | 42(1) | 38(1) | -6(1) | 4(1) | -12(1) |
| C(13) | 42(1) | 41(1) | 44(1) | -1(1) | 11(1) | -14(1) |
| C(14) | 39(1) | 37(1) | 53(2) | -1(1) | 6(1) | -17(1) |
| C(15) | 36(1) | 34(1) | 46(1) | -2(1) | -1(1) | -15(1) |
| C(16) | 32(1) | 29(1) | 40(1) | -2(1) | 2(1) | -12(1) |
| C(17) | 51(2) | 61(2) | 39(1) | -7(1) | 8(1) | -24(1) |
| C(18) | 59(2) | 62(2) | 65(2) | 2(2) | 6(1) | -38(2) |
| C(21) | 34(1) | 27(1) | 38(1) | 0(1) | -2(1) | -9(1) |
| C(22) | 34(1) | 36(1) | 47(1) | 5(1) | -2(1) | -13(1) |
| C(23) | 34(1) | 39(1) | 51(2) | 2(1) | 5(1) | -10(1) |
| C(24) | 43(1) | 33(1) | 39(1) | 1(1) | 4(1) | -9(1) |
| C(25) | 42(1) | 29(1) | 36(1) | 2(1) | -1(1) | -13(1) |
| C(26) | 35(1) | 27(1) | 32(1) | 3(1) | -2(1) | -10(1) |
| C(27) | 35(1) | 48(2) | 78(2) | -5(1) | -1(1) | -19(1) |
| C(28) | 53(2) | 41(2) | 59(2) | -7(1) | 12(1) | -12(1) |
| C(31) | 33(1) | 29(1) | 41(1) | 1(1) | 1(1) | -16(1) |
| C(32) | 31(1) | 28(1) | 53(1) | -2(1) | 5(1) | -13(1) |
| C(33) | 32(1) | 28(1) | 59(2) | 6(1) | 0(1) | -11(1) |
| C(34) | 35(1) | 36(1) | 47(1) | 8(1) | -4(1) | -19(1) |
| C(35) | 39(1) | 31(1) | 41(1) | 4(1) | -1(1) | -18(1) |
| C(36) | 32(1) | 25(1) | 39(1) | 2(1) | 0(1) | -12(1) |
| C(37) | 43(1) | 31(1) | 65(2) | -7(1) | 4(1) | -11(1) |

**Table 5** *(cont)*

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| C(38) | 46(1) | 44(2) | 55(2) | 11(1) | -12(1) | -20(1) |
| C(41) | 53(2) | 69(2) | 81(2) | -39(2) | 8(2) | -34(2) |
| C(42) | 84(3) | 126(4) | 75(2) | -54(2) | 12(2) | -48(3) |
| C(43) | 67(2) | 51(2) | 140(3) | -36(2) | 13(2) | -33(2) |
| C(51) | 44(1) | 29(1) | 36(1) | 2(1) | -3(1) | -19(1) |
| C(52) | 45(1) | 35(1) | 46(1) | 5(1) | -5(1) | -22(1) |
| C(53) | 55(2) | 41(1) | 52(2) | 4(1) | -12(1) | -31(1) |
| C(54) | 57(2) | 34(1) | 40(1) | 0(1) | -9(1) | -24(1) |
| C(55) | 46(1) | 31(1) | 37(1) | 0(1) | -5(1) | -16(1) |
| C(56) | 42(1) | 28(1) | 33(1) | 4(1) | -5(1) | -17(1) |
| C(57) | 45(2) | 46(2) | 79(2) | -5(1) | 2(1) | -28(1) |
| C(58) | 68(2) | 44(2) | 59(2) | -9(1) | -10(1) | -31(1) |
| C(61) | 53(2) | 35(1) | 41(1) | -3(1) | -7(1) | -26(1) |
| C(62) | 68(2) | 41(1) | 42(1) | -2(1) | -12(1) | -32(1) |
| C(63) | 82(2) | 39(2) | 47(2) | 4(1) | -29(2) | -30(2) |
| C(64) | 58(2) | 32(1) | 64(2) | -2(1) | -26(1) | -16(1) |
| C(65) | 45(1) | 30(1) | 57(2) | -5(1) | -8(1) | -15(1) |
| C(66) | 41(1) | 27(1) | 47(1) | 0(1) | -9(1) | -16(1) |
| C(67) | 94(2) | 74(2) | 38(2) | -3(1) | -8(2) | -51(2) |
| C(68) | 65(2) | 49(2) | 96(3) | -4(2) | -40(2) | -12(2) |
| C(71) | 33(1) | 32(1) | 39(1) | 3(1) | -3(1) | -14(1) |
| C(72) | 35(1) | 30(1) | 49(1) | 3(1) | -7(1) | -14(1) |
| C(73) | 39(1) | 35(1) | 54(2) | 9(1) | -6(1) | -20(1) |
| C(74) | 37(1) | 40(1) | 44(1) | 10(1) | -6(1) | -18(1) |
| C(75) | 34(1) | 36(1) | 39(1) | 3(1) | -4(1) | -13(1) |
| C(76) | 34(1) | 28(1) | 39(1) | 3(1) | -5(1) | -13(1) |
| C(77) | 49(2) | 31(1) | 62(2) | -1(1) | -1(1) | -18(1) |
| C(78) | 49(2) | 50(2) | 51(2) | 12(1) | 2(1) | -22(1) |
| C(81) | 42(1) | 56(2) | 66(2) | -21(1) | 17(1) | -23(1) |
| C(82) | 58(2) | 44(2) | 104(3) | -20(2) | 24(2) | -19(2) |
| C(83) | 68(2) | 86(2) | 64(2) | -34(2) | 19(2) | -37(2) |

## 2.2 Crystal Structure Data for (*rac*)-231




(*rac*)-**231**

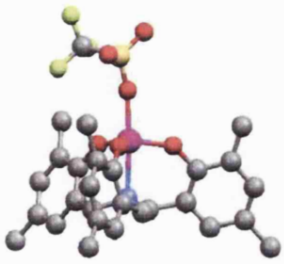


**Figure 2** *Complex (rac)-**231** and its crystal structure*

**Table 6**

| Empirical formula | $C_{30}H_{32}F_3NO_6STi$ |
|---|---|
| Formula weight | 636.52 |
| Temperature | 150(2) K |
| Wavelength | 0.71070 Å |
| Crystal system | Triclinic |
| Space group | P-1 |
| Unit cell dimensions | a = 10.1340(2) Å α = 101.6130(10)°<br>b = 16.8420(3) Å β = 93.7620(10)°<br>c = 18.2010(4) Å γ = 95.2590(10)° |
| Volume | 3018.81(10) $Å^3$ |
| Z | 4 |
| Density (calculated) | 1.401 $Mg/m^3$ |
| Absorption coefficient | 0.414 $mm^{-1}$ |
| F(000) | 1322 |
| Crystal size | 0.22 x 0.20 x 0.15 $mm^3$ |
| Theta range for data collection | 3.59 to 25.03° |
| Index ranges | 0<=h<=12, -20<=k<=19, -21<=l<=21 |
| Reflections collected | 41484 |
| Independent reflections | 10600 [R(int) = 0.0420] |
| Completeness to theta = 25.03° | 99.4% |
| Max. and min. transmission | 0.9405 and 0.9145 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 10600 / 0 / 786 |
| Goodness-of-fit on F2 | 1.026 |
| Final R indices [I>2sigma(I)] | R1 = 0.0436, wR2 = 0.1056 |
| R indices (all data) | R1 = 0.0630, wR2 = 0.1159 |
| Extinction coefficient | 0.0023(4) |
| Largest diff. peak and hole | 0.502 and -0.373 $e.Å^{-3}$ |

**Table 7** *Atomic coordinates (× $10^4$) and equivalent isotropic displacement parameters ($Å^2$ × $10^3$) for (R)-**231***

| | x | y | z | U(eq)[a] |
|---|---|---|---|---|
| Ti(1) | 3664(1) | 7123(1) | 8417(1) | 30(1) |
| Ti(2) | 8294(1) | 8042(1) | 3575(1) | 38(1) |
| F(1) | 7367(2) | 8293(1) | 8922(1) | 70(1) |
| F(2) | 7994(2) | 7108(1) | 8908(1) | 63(1) |
| F(3) | 8644(2) | 8091(1) | 9847(1) | 63(1) |
| F(4) | 10078(3) | 9394(2) | 6526(1) | 110(1) |
| F(5) | 8037(3) | 9072(2) | 6129(2) | 102(1) |
| F(6) | 9310(3) | 9772(1) | 5555(1) | 96(1) |
| N(1) | 2049(2) | 7109(1) | 7531(1) | 31(1) |
| N(2) | 7651(2) | 7903(1) | 2366(1) | 34(1) |
| O(1) | 2815(2) | 6170(1) | 8508(1) | 42(1) |
| O(2) | 3009(2) | 8029(1) | 8887(1) | 39(1) |
| O(3) | 4731(2) | 7118(1) | 7658(1) | 37(1) |
| O(4A) | 5181(2) | 7166(1) | 9190(1) | 39(1) |
| O(4B) | 5902(2) | 8282(1) | 10253(1) | 59(1) |
| O(4C) | 6544(2) | 6921(1) | 10236(1) | 60(1) |
| O(5) | 9944(2) | 8047(1) | 3266(1) | 44(1) |
| O(6) | 7249(2) | 7088(1) | 3472(1) | 41(1) |
| O(7) | 7624(2) | 9007(1) | 3674(1) | 46(1) |
| O(8A) | 8697(2) | 8115(1) | 4688(1) | 56(1) |
| O(8B) | 10988(2) | 8404(2) | 5156(1) | 72(1) |
| O(8C) | 9418(3) | 7642(1) | 5792(1) | 72(1) |
| S(1) | 6176(1) | 7520(1) | 9832(1) | 41(1) |
| S(2) | 9666(1) | 8232(1) | 5343(1) | 48(1) |
| C(1) | 1748(3) | 6259(2) | 7063(2) | 42(1) |
| C(2) | 802(2) | 7371(2) | 7861(2) | 39(1) |
| C(3) | 2461(2) | 7670(2) | 7024(2) | 38(1) |
| C(4) | 7627(3) | 7759(2) | 9349(2) | 46(1) |
| C(5) | 8448(2) | 7305(2) | 1908(2) | 37(1) |
| C(6) | 6200(2) | 7590(2) | 2209(2) | 37(1) |
| C(7) | 7837(3) | 8706(2) | 2122(2) | 40(1) |
| C(8) | 9247(4) | 9171(2) | 5914(2) | 65(1) |
| C(11) | 1736(2) | 5619(2) | 8206(2) | 41(1) |
| C(12) | 1247(3) | 5064(2) | 8620(2) | 47(1) |
| C(13) | 125(3) | 4539(2) | 8294(2) | 53(1) |
| C(14) | -493(3) | 4550(2) | 7596(2) | 54(1) |
| C(15) | 39(3) | 5115(2) | 7195(2) | 49(1) |
| C(16) | 1156(3) | 5654(2) | 7499(2) | 42(1) |
| C(17) | 1918(4) | 5031(2) | 9370(2) | 66(1) |
| C(18) | -1692(3) | 3952(2) | 7249(2) | 72(1) |

[a] U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

**Table 7** *(cont)*

| | x | y | z | U(eq)[a] |
|---|---|---|---|---|
| C(21) | 2041(3) | 8536(2) | 8819(2) | 37(1) |
| C(22) | 2170(3) | 9310(2) | 9273(2) | 44(1) |
| C(23) | 1187(3) | 9808(2) | 9157(2) | 51(1) |
| C(24) | 135(3) | 9567(2) | 8615(2) | 47(1) |
| C(25) | 19(3) | 8774(2) | 8178(2) | 43(1) |
| C(26) | 961(2) | 8245(2) | 8285(2) | 38(1) |
| C(27) | 3332(3) | 9596(2) | 9850(2) | 63(1) |
| C(28) | -896(3) | 10138(2) | 8501(2) | 65(1) |
| C(31) | 4733(2) | 7188(2) | 6920(1) | 36(1) |
| C(32) | 5864(2) | 7046(2) | 6538(2) | 40(1) |
| C(33) | 5826(3) | 7138(2) | 5796(2) | 46(1) |
| C(34) | 4709(3) | 7346(2) | 5425(2) | 48(1) |
| C(35) | 3609(3) | 7487(2) | 5827(2) | 46(1) |
| C(36) | 3608(3) | 7424(2) | 6575(1) | 38(1) |
| C(37) | 7085(3) | 6819(2) | 6933(2) | 57(1) |
| C(38) | 4700(4) | 7445(3) | 4617(2) | 71(1) |
| C(51) | 10607(2) | 7971(2) | 2626(2) | 38(1) |
| C(52) | 11957(3) | 8262(2) | 2683(2) | 43(1) |
| C(53) | 12577(3) | 8143(2) | 2012(2) | 49(1) |
| C(54) | 11926(3) | 7768(2) | 1321(2) | 48(1) |
| C(55) | 10564(3) | 7517(2) | 1289(2) | 42(1) |
| C(56) | 9900(2) | 7615(2) | 1940(2) | 38(1) |
| C(57) | 12672(3) | 8675(2) | 3427(2) | 60(1) |
| C(58) | 12638(3) | 7630(2) | 612(2) | 70(1) |
| C(61) | 6406(2) | 6521(2) | 2969(2) | 38(1) |
| C(62) | 6091(3) | 5748(2) | 3115(2) | 43(1) |
| C(63) | 5245(3) | 5197(2) | 2578(2) | 49(1) |
| C(64) | 4723(3) | 5385(2) | 1918(2) | 50(1) |
| C(65) | 5065(3) | 6163(2) | 1795(2) | 45(1) |
| C(66) | 5897(2) | 6739(2) | 2317(2) | 38(1) |
| C(67) | 6651(3) | 5532(2) | 3826(2) | 56(1) |
| C(68) | 3791(4) | 4772(2) | 1349(2) | 70(1) |
| C(71) | 6931(3) | 9467(2) | 3275(2) | 44(1) |
| C(72) | 6214(3) | 10063(2) | 3653(2) | 51(1) |
| C(73) | 5449(3) | 10466(2) | 3216(2) | 55(1) |
| C(74) | 5396(3) | 10302(2) | 2434(2) | 53(1) |
| C(75) | 6165(3) | 9723(2) | 2078(2) | 46(1) |
| C(76) | 6949(2) | 9309(2) | 2490(2) | 40(1) |
| C(77) | 6314(4) | 10249(2) | 4500(2) | 70(1) |
| C(78) | 4534(3) | 10742(2) | 1976(2) | 71(1) |

[a] U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

**Table 7** *(cont)*

| | x | y | z | U(eq)[a] |
|---|---|---|---|---|
| C(91) | 1625(9) | 5168(8) | 4706(6) | 108(5) |
| C(92) | 909(12) | 5837(6) | 4878(6) | 110(6) |
| C(93) | -394(12) | 5731(7) | 5065(6) | 131(8) |
| C(94) | -981(8) | 4956(7) | 5080(6) | 127(7) |
| C(95) | -265(8) | 4287(6) | 4908(6) | 85(4) |
| C(96) | 1039(8) | 4393(7) | 4721(6) | 82(3) |
| C(97) | 2974(14) | 5304(7) | 4527(6) | 129(4) |

[a] U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

**Table 8** *Bond Lengths for (rac)-**231***

| Bond | Length /Å | Bond | Length /Å |
|---|---|---|---|
| Ti(1)-O(1) | 1.7932(17) | O(6)-C(61) | 1.370(3) |
| Ti(1)-O(2) | 1.7986(17) | O(7)-C(71) | 1.371(3) |
| Ti(1)-O(3) | 1.8082(17) | O(8A)-S(2) | 1.463(2) |
| Ti(1)-O(4A) | 2.0016(17) | O(8B)-S(2) | 1.423(2) |
| Ti(1)-N(1) | 2.216(2) | O(8C)-S(2) | 1.423(2) |
| Ti(2)-O(5) | 1.7988(18) | S(1)-C(4) | 1.817(3) |
| Ti(2)-O(7) | 1.799(2) | S(2)-C(8) | 1.812(4) |
| Ti(2)-O(6) | 1.8109(18) | C(1)-C(16) | 1.516(4) |
| Ti(2)-O(8A) | 2.017(2) | C(2)-C(26) | 1.507(4) |
| Ti(2)-N(2) | 2.213(2) | C(3)-C(36) | 1.506(3) |
| F(1)-C(4) | 1.334(3) | C(5)-C(56) | 1.508(4) |
| F(2)-C(4) | 1.321(3) | C(6)-C(66) | 1.493(4) |
| F(3)-C(4) | 1.328(3) | C(7)-C(76) | 1.503(4) |
| F(4)-C(8) | 1.319(4) | C(11)-C(12) | 1.391(4) |
| F(5)-C(8) | 1.318(4) | C(11)-C(16) | 1.395(4) |
| F(6)-C(8) | 1.309(4) | C(12)-C(13) | 1.394(4) |
| N(1)-C(2) | 1.499(3) | C(12)-C(17) | 1.498(4) |
| N(1)-C(3) | 1.499(3) | C(13)-C(14) | 1.382(5) |
| N(1)-C(1) | 1.505(3) | C(14)-C(15) | 1.402(4) |
| N(2)-C(5) | 1.504(3) | C(14)-C(18) | 1.520(4) |
| N(2)-C(6) | 1.505(3) | C(15)-C(16) | 1.393(4) |
| N(2)-C(7) | 1.506(3) | C(21)-C(22) | 1.386(4) |
| O(1)-C(11) | 1.374(3) | C(21)-C(26) | 1.397(4) |
| O(2)-C(21) | 1.373(3) | C(22)-C(23) | 1.391(4) |
| O(3)-C(31) | 1.372(3) | C(22)-C(27) | 1.501(4) |
| O(4A)-S(1) | 1.4797(18) | C(23)-C(24) | 1.378(4) |
| O(4B)-S(1) | 1.417(2) | C(24)-C(25) | 1.400(4) |
| O(4C)-S(1) | 1.425(2) | C(24)-C(28) | 1.515(4) |
| O(5)-C(51) | 1.372(3) | C(25)-C(26) | 1.394(4) |

**Table 8** *(cont)*

| Bond | Length /Å | Bond | Length /Å |
|---|---|---|---|
| C(31)-C(36) | 1.393(4) | C(63)-C(64) | 1.386(4) |
| C(31)-C(32) | 1.394(4) | C(64)-C(65) | 1.390(4) |
| C(32)-C(33) | 1.390(4) | C(64)-C(68) | 1.514(4) |
| C(32)-C(37) | 1.506(4) | C(65)-C(66) | 1.389(4) |
| C(33)-C(34) | 1.388(4) | C(71)-C(72) | 1.389(4) |
| C(34)-C(35) | 1.384(4) | C(71)-C(76) | 1.402(4) |
| C(34)-C(38) | 1.514(4) | C(72)-C(73) | 1.388(5) |
| C(35)-C(36) | 1.388(4) | C(72)-C(77) | 1.506(5) |
| C(51)-C(56) | 1.390(4) | C(73)-C(74) | 1.390(5) |
| C(51)-C(52) | 1.400(4) | C(74)-C(75) | 1.389(4) |
| C(52)-C(53) | 1.397(4) | C(74)-C(78) | 1.509(5) |
| C(52)-C(57) | 1.497(4) | C(75)-C(76) | 1.383(4) |
| C(53)-C(54) | 1.382(4) | C(91)-C(92) | 1.3900 |
| C(54)-C(55) | 1.400(4) | C(91)-C(96) | 1.3900 |
| C(54)-C(58) | 1.508(4) | C(91)-C(97) | 1.434(15) |
| C(55)-C(56) | 1.390(4) | C(92)-C(93) | 1.3900 |
| C(61)-C(66) | 1.392(4) | C(93)-C(94) | 1.3900 |
| C(61)-C(62) | 1.393(4) | C(94)-C(95) | 1.3900 |
| C(62)-C(63) | 1.390(4) | C(95)-C(96) | 1.3900 |
| C(62)-C(67) | 1.503(4) | | |

**Table 9** *Bond Angles for (rac)-**231***

| Bond | Angle /° | Bond | Angle /° |
|---|---|---|---|
| O(1)-Ti(1)-O(2) | 116.34(9) | O(7)-Ti(2)-N(2) | 84.41(8) |
| O(1)-Ti(1)-O(3) | 118.03(9) | O(6)-Ti(2)-N(2) | 83.16(8) |
| O(2)-Ti(1)-O(3) | 122.74(9) | O(8A)-Ti(2)-N(2) | 174.26(8) |
| O(1)-Ti(1)-O(4A) | 97.34(8) | C(2)-N(1)-C(3) | 108.13(19) |
| O(2)-Ti(1)-O(4A) | 96.17(8) | C(2)-N(1)-C(1) | 108.62(19) |
| O(3)-Ti(1)-O(4A) | 93.61(7) | C(3)-N(1)-C(1) | 108.4(2) |
| O(1)-Ti(1)-N(1) | 85.05(8) | C(2)-N(1)-Ti(1) | 111.75(15) |
| O(2)-Ti(1)-N(1) | 83.94(8) | C(3)-N(1)-Ti(1) | 110.64(14) |
| O(3)-Ti(1)-N(1) | 84.05(7) | C(1)-N(1)-Ti(1) | 109.21(15) |
| O(4A)-Ti(1)-N(1) | 177.25(7) | C(5)-N(2)-C(6) | 108.74(19) |
| O(5)-Ti(2)-O(7) | 114.34(9) | C(5)-N(2)-C(7) | 109.40(19) |
| O(5)-Ti(2)-O(6) | 120.05(9) | C(6)-N(2)-C(7) | 107.42(19) |
| O(7)-Ti(2)-O(6) | 122.38(9) | C(5)-N(2)-Ti(2) | 109.25(15) |
| O(5)-Ti(2)-O(8A) | 100.67(8) | C(6)-N(2)-Ti(2) | 110.68(15) |
| O(7)-Ti(2)-O(8A) | 95.52(9) | C(7)-N(2)-Ti(2) | 111.30(15) |
| O(6)-Ti(2)-O(8A) | 92.07(9) | C(11)-O(1)-Ti(1) | 141.94(17) |
| O(5)-Ti(2)-N(2) | 84.54(8) | C(21)-O(2)-Ti(1) | 143.15(16) |

**Table 9** *(cont)*

| Bond | Angle /° | Bond | Angle /° |
|---|---|---|---|
| C(31)-O(3)-Ti(1) | 142.62(16) | C(14)-C(13)-C(12) | 123.4(3) |
| S(1)-O(4A)-Ti(1) | 158.14(12) | C(13)-C(14)-C(15) | 118.4(3) |
| C(51)-O(5)-Ti(2) | 141.71(17) | C(13)-C(14)-C(18) | 121.8(3) |
| C(61)-O(6)-Ti(2) | 143.16(17) | C(15)-C(14)-C(18) | 119.8(3) |
| C(71)-O(7)-Ti(2) | 142.04(18) | C(16)-C(15)-C(14) | 120.4(3) |
| S(2)-O(8A)-Ti(2) | 149.78(14) | C(15)-C(16)-C(11) | 118.8(3) |
| O(4B)-S(1)-O(4C) | 117.84(14) | C(15)-C(16)-C(1) | 120.7(3) |
| O(4B)-S(1)-O(4A) | 114.02(12) | C(11)-C(16)-C(1) | 120.5(2) |
| O(4C)-S(1)-O(4A) | 111.61(12) | O(2)-C(21)-C(22) | 119.4(2) |
| O(4B)-S(1)-C(4) | 104.71(13) | O(2)-C(21)-C(26) | 118.0(2) |
| O(4C)-S(1)-C(4) | 105.02(14) | C(22)-C(21)-C(26) | 122.6(2) |
| O(4A)-S(1)-C(4) | 101.51(12) | C(21)-C(22)-C(23) | 116.8(3) |
| O(8B)-S(2)-O(8C) | 118.57(16) | C(21)-C(22)-C(27) | 121.1(3) |
| O(8B)-S(2)-O(8A) | 111.90(14) | C(23)-C(22)-C(27) | 122.0(3) |
| O(8C)-S(2)-O(8A) | 112.61(14) | C(24)-C(23)-C(22) | 123.0(3) |
| O(8B)-S(2)-C(8) | 105.76(17) | C(23)-C(24)-C(25) | 118.6(3) |
| O(8C)-S(2)-C(8) | 104.13(16) | C(23)-C(24)-C(28) | 121.0(3) |
| O(8A)-S(2)-C(8) | 101.83(15) | C(25)-C(24)-C(28) | 120.4(3) |
| N(1)-C(1)-C(16) | 113.1(2) | C(26)-C(25)-C(24) | 120.5(3) |
| N(1)-C(2)-C(26) | 113.0(2) | C(25)-C(26)-C(21) | 118.3(3) |
| N(1)-C(3)-C(36) | 114.5(2) | C(25)-C(26)-C(2) | 121.4(2) |
| F(2)-C(4)-F(3) | 108.3(2) | C(21)-C(26)-C(2) | 120.3(2) |
| F(2)-C(4)-F(1) | 107.8(3) | O(3)-C(31)-C(36) | 118.8(2) |
| F(3)-C(4)-F(1) | 108.2(2) | O(3)-C(31)-C(32) | 119.7(2) |
| F(2)-C(4)-S(1) | 112.4(2) | C(36)-C(31)-C(32) | 121.4(2) |
| F(3)-C(4)-S(1) | 110.1(2) | C(33)-C(32)-C(31) | 117.6(2) |
| F(1)-C(4)-S(1) | 109.98(19) | C(33)-C(32)-C(37) | 122.0(2) |
| N(2)-C(5)-C(56) | 113.1(2) | C(31)-C(32)-C(37) | 120.4(2) |
| C(66)-C(6)-N(2) | 113.5(2) | C(34)-C(33)-C(32) | 122.6(3) |
| C(76)-C(7)-N(2) | 112.7(2) | C(35)-C(34)-C(33) | 117.9(3) |
| F(6)-C(8)-F(5) | 108.4(3) | C(35)-C(34)-C(38) | 120.7(3) |
| F(6)-C(8)-F(4) | 107.5(3) | C(33)-C(34)-C(38) | 121.4(3) |
| F(5)-C(8)-F(4) | 107.7(3) | C(34)-C(35)-C(36) | 121.7(3) |
| F(6)-C(8)-S(2) | 112.2(2) | C(35)-C(36)-C(31) | 118.7(2) |
| F(5)-C(8)-S(2) | 110.6(2) | C(35)-C(36)-C(3) | 120.8(2) |
| F(4)-C(8)-S(2) | 110.2(3) | C(31)-C(36)-C(3) | 120.4(2) |
| O(1)-C(11)-C(12) | 119.2(3) | O(5)-C(51)-C(56) | 118.3(2) |
| O(1)-C(11)-C(16) | 118.1(2) | O(5)-C(51)-C(52) | 119.3(2) |
| C(12)-C(11)-C(16) | 122.7(2) | C(56)-C(51)-C(52) | 122.4(2) |
| C(11)-C(12)-C(13) | 116.4(3) | C(53)-C(52)-C(51) | 116.1(3) |
| C(11)-C(12)-C(17) | 121.1(3) | C(53)-C(52)-C(57) | 122.9(3) |
| C(13)-C(12)-C(17) | 122.5(3) | C(51)-C(52)-C(57) | 120.9(3) |

**Table 9** *(cont)*

| Bond | Angle /° | Bond | Angle /° |
|---|---|---|---|
| C(54)-C(53)-C(52) | 123.5(3) | O(7)-C(71)-C(72) | 119.6(3) |
| C(53)-C(54)-C(55) | 118.3(3) | O(7)-C(71)-C(76) | 118.5(2) |
| C(53)-C(54)-C(58) | 121.9(3) | C(72)-C(71)-C(76) | 121.8(3) |
| C(55)-C(54)-C(58) | 119.8(3) | C(73)-C(72)-C(71) | 117.1(3) |
| C(56)-C(55)-C(54) | 120.6(3) | C(73)-C(72)-C(77) | 123.5(3) |
| C(55)-C(56)-C(51) | 119.0(2) | C(71)-C(72)-C(77) | 119.4(3) |
| C(55)-C(56)-C(5) | 120.4(2) | C(72)-C(73)-C(74) | 122.8(3) |
| C(51)-C(56)-C(5) | 120.5(2) | C(75)-C(74)-C(73) | 118.4(3) |
| O(6)-C(61)-C(66) | 118.2(2) | C(75)-C(74)-C(78) | 120.3(3) |
| O(6)-C(61)-C(62) | 119.8(2) | C(73)-C(74)-C(78) | 121.3(3) |
| C(66)-C(61)-C(62) | 122.0(2) | C(76)-C(75)-C(74) | 120.9(3) |
| C(63)-C(62)-C(61) | 117.0(3) | C(75)-C(76)-C(71) | 118.9(3) |
| C(63)-C(62)-C(67) | 122.2(3) | C(75)-C(76)-C(7) | 122.0(3) |
| C(61)-C(62)-C(67) | 120.7(3) | C(71)-C(76)-C(7) | 119.1(2) |
| C(64)-C(63)-C(62) | 123.0(3) | C(92)-C(91)-C(96) | 120.0 |
| C(63)-C(64)-C(65) | 118.0(3) | C(92)-C(91)-C(97) | 118.3(9) |
| C(63)-C(64)-C(68) | 121.6(3) | C(96)-C(91)-C(97) | 121.7(9) |
| C(65)-C(64)-C(68) | 120.4(3) | C(93)-C(92)-C(91) | 120.0 |
| C(66)-C(65)-C(64) | 121.3(3) | C(92)-C(93)-C(94) | 120.0 |
| C(65)-C(66)-C(61) | 118.7(3) | C(95)-C(94)-C(93) | 120.0 |
| C(65)-C(66)-C(6) | 121.4(2) | C(94)-C(95)-C(96) | 120.0 |
| C(61)-C(66)-C(6) | 119.8(2) | C(95)-C(96)-C(91) | 120.0 |

**Table10** *Anisotropic displacement parameters ($Å^2$ × 103) for (R)-**231**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$*

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| Ti(1) | 27(1) | 31(1) | 30(1) | 2(1) | 1(1) | -1(1) |
| Ti(2) | 34(1) | 45(1) | 31(1) | 1(1) | 4(1) | 1(1) |
| F(1) | 58(1) | 78(1) | 86(1) | 42(1) | 14(1) | 3(1) |
| F(2) | 45(1) | 61(1) | 75(1) | -10(1) | 14(1) | 6(1) |
| F(3) | 35(1) | 65(1) | 76(1) | -4(1) | -8(1) | -9(1) |
| F(4) | 156(2) | 92(2) | 58(1) | -10(1) | -21(2) | -34(2) |
| F(5) | 107(2) | 83(2) | 111(2) | -6(1) | 56(2) | 6(1) |
| F(6) | 149(2) | 49(1) | 92(2) | 18(1) | 23(2) | 8(1) |
| N(1) | 28(1) | 30(1) | 33(1) | 1(1) | 2(1) | -1(1) |
| N(2) | 28(1) | 38(1) | 35(1) | 4(1) | 5(1) | 3(1) |
| O(1) | 37(1) | 38(1) | 49(1) | 11(1) | -3(1) | -5(1) |
| O(2) | 39(1) | 37(1) | 37(1) | -3(1) | -2(1) | 6(1) |
| O(3) | 29(1) | 49(1) | 32(1) | 5(1) | 2(1) | 3(1) |
| O(4A) | 31(1) | 47(1) | 34(1) | 4(1) | -3(1) | -1(1) |
| O(4B) | 51(1) | 57(1) | 56(1) | -16(1) | 10(1) | -1(1) |

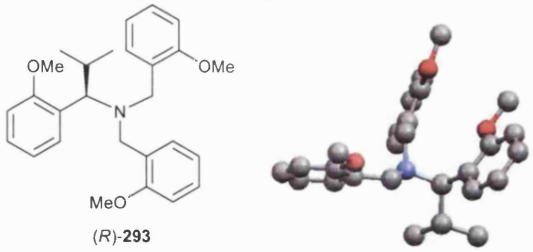
**Table 10** *(cont)*

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| O(4C) | 67(1) | 65(1) | 47(1) | 23(1) | -18(1) | -6(1) |
| O(5) | 32(1) | 62(1) | 36(1) | 6(1) | 2(1) | 1(1) |
| O(6) | 42(1) | 45(1) | 33(1) | 4(1) | 5(1) | -1(1) |
| O(7) | 49(1) | 44(1) | 41(1) | -1(1) | 6(1) | 4(1) |
| O(8A) | 51(1) | 76(2) | 35(1) | 2(1) | -2(1) | 3(1) |
| O(8B) | 44(1) | 97(2) | 77(2) | 22(1) | 0(1) | -1(1) |
| O(8C) | 98(2) | 54(1) | 66(2) | 28(1) | 3(1) | -4(1) |
| S(1) | 36(1) | 46(1) | 35(1) | 0(1) | -2(1) | -2(1) |
| S(2) | 51(1) | 49(1) | 40(1) | 9(1) | -2(1) | -2(1) |
| C(1) | 36(1) | 40(2) | 41(2) | -7(1) | -2(1) | 1(1) |
| C(2) | 28(1) | 44(2) | 42(2) | 2(1) | 3(1) | 1(1) |
| C(3) | 35(1) | 40(2) | 38(2) | 7(1) | 2(1) | 2(1) |
| C(4) | 35(2) | 45(2) | 53(2) | 0(1) | 1(1) | 1(1) |
| C(5) | 35(1) | 42(2) | 31(1) | 3(1) | 5(1) | 6(1) |
| C(6) | 28(1) | 43(2) | 38(2) | 4(1) | 3(1) | 1(1) |
| C(7) | 37(1) | 40(2) | 41(2) | 7(1) | 4(1) | 1(1) |
| C(8) | 91(3) | 52(2) | 46(2) | 7(2) | 7(2) | -9(2) |
| C(11) | 32(1) | 32(1) | 54(2) | 3(1) | 0(1) | -2(1) |
| C(12) | 41(2) | 34(2) | 67(2) | 11(1) | 11(1) | 3(1) |
| C(13) | 42(2) | 35(2) | 85(2) | 17(2) | 15(2) | 2(1) |
| C(14) | 32(2) | 32(2) | 93(3) | 5(2) | 6(2) | 0(1) |
| C(15) | 34(2) | 39(2) | 68(2) | -2(2) | -2(1) | 0(1) |
| C(16) | 34(1) | 31(1) | 55(2) | -4(1) | 6(1) | 2(1) |
| C(17) | 72(2) | 54(2) | 75(2) | 31(2) | 2(2) | -6(2) |
| C(18) | 41(2) | 44(2) | 123(3) | 12(2) | -5(2) | -9(1) |
| C(21) | 37(1) | 34(1) | 41(2) | 5(1) | 7(1) | 4(1) |
| C(22) | 40(2) | 36(2) | 52(2) | -1(1) | 10(1) | -2(1) |
| C(23) | 48(2) | 30(2) | 71(2) | -1(1) | 21(2) | 0(1) |
| C(24) | 39(2) | 36(2) | 71(2) | 14(2) | 20(2) | 6(1) |
| C(25) | 33(1) | 43(2) | 56(2) | 12(1) | 11(1) | 5(1) |
| C(26) | 34(1) | 38(2) | 42(2) | 7(1) | 9(1) | 3(1) |
| C(27) | 61(2) | 44(2) | 69(2) | -18(2) | -3(2) | 0(2) |
| C(28) | 46(2) | 42(2) | 109(3) | 18(2) | 22(2) | 11(1) |
| C(31) | 35(1) | 40(2) | 30(1) | 2(1) | 3(1) | 2(1) |
| C(32) | 32(1) | 46(2) | 39(2) | 4(1) | 5(1) | 2(1) |
| C(33) | 42(2) | 57(2) | 38(2) | 5(1) | 13(1) | 11(1) |
| C(34) | 55(2) | 59(2) | 32(2) | 7(1) | 10(1) | 17(1) |
| C(35) | 45(2) | 56(2) | 36(2) | 5(1) | 2(1) | 13(1) |
| C(36) | 38(1) | 40(2) | 33(1) | 3(1) | 5(1) | 4(1) |
| C(37) | 35(2) | 91(3) | 49(2) | 18(2) | 9(1) | 12(2) |
| C(38) | 81(2) | 102(3) | 40(2) | 21(2) | 19(2) | 44(2) |
| C(51) | 31(1) | 44(2) | 42(2) | 12(1) | 5(1) | 5(1) |

**Table 10** *(cont)*

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| C(52) | 32(1) | 43(2) | 58(2) | 17(1) | 3(1) | 8(1) |
| C(53) | 32(1) | 51(2) | 71(2) | 28(2) | 11(1) | 11(1) |
| C(54) | 46(2) | 49(2) | 62(2) | 29(2) | 23(2) | 20(1) |
| C(55) | 44(2) | 44(2) | 45(2) | 16(1) | 12(1) | 15(1) |
| C(56) | 34(1) | 41(2) | 42(2) | 12(1) | 9(1) | 9(1) |
| C(57) | 38(2) | 66(2) | 73(2) | 18(2) | -6(2) | -4(1) |
| C(58) | 61(2) | 86(3) | 77(2) | 32(2) | 36(2) | 22(2) |
| C(61) | 34(1) | 41(2) | 36(2) | 0(1) | 9(1) | 1(1) |
| C(62) | 45(2) | 43(2) | 42(2) | 5(1) | 13(1) | 9(1) |
| C(63) | 47(2) | 35(2) | 62(2) | 4(1) | 13(2) | 4(1) |
| C(64) | 42(2) | 43(2) | 58(2) | -4(1) | 2(1) | -1(1) |
| C(65) | 39(2) | 46(2) | 45(2) | 2(1) | 1(1) | 2(1) |
| C(66) | 31(1) | 41(2) | 39(2) | 0(1) | 6(1) | 2(1) |
| C(67) | 71(2) | 46(2) | 52(2) | 10(2) | 11(2) | 12(2) |
| C(68) | 72(2) | 44(2) | 80(3) | -7(2) | -12(2) | -10(2) |
| C(71) | 34(1) | 39(2) | 56(2) | 2(1) | 7(1) | -6(1) |
| C(72) | 41(2) | 34(2) | 72(2) | -4(2) | 23(2) | -8(1) |
| C(73) | 36(2) | 30(2) | 96(3) | 0(2) | 22(2) | -2(1) |
| C(74) | 32(2) | 32(2) | 90(3) | 3(2) | 1(2) | -5(1) |
| C(75) | 35(1) | 36(2) | 63(2) | 5(1) | -1(1) | -4(1) |
| C(76) | 32(1) | 35(2) | 50(2) | 3(1) | 3(1) | -3(1) |
| C(77) | 85(3) | 52(2) | 74(2) | 3(2) | 45(2) | 4(2) |
| C(78) | 44(2) | 45(2) | 119(3) | 7(2) | -8(2) | 6(1) |
| C(91) | 151(12) | 87(9) | 70(8) | 20(7) | -68(8) | -23(9) |
| C(92) | 161(15) | 89(9) | 59(8) | -26(6) | -53(8) | 48(9) |
| C(93) | 190(20) | 77(10) | 100(11) | -42(9) | -82(11) | 73(11) |
| C(94) | 206(17) | 105(12) | 60(7) | -16(7) | -51(9) | 79(13) |
| C(95) | 130(13) | 72(7) | 46(6) | -5(5) | -31(6) | 45(6) |
| C(96) | 106(8) | 62(6) | 70(7) | 4(5) | -37(6) | 14(6) |
| C(97) | 179(12) | 108(8) | 86(7) | 27(6) | -22(8) | -43(8) |

## 2.3 Crystal Structure Data for (*R*)-299




(*R*)-**293**

**Figure 3** *Amine (R)-**299** and its crystal structure*

**Table 11** *Crystal data and structure refinement for (R)-**299***

| | | |
|---|---|---|
| Empirical formula | $C_{27}H_{33}NO_3$ | |
| Formula weight | 419.54 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | P 21 21 21 | |
| Unit cell dimensions | a = 10.78400(10) Å | $\alpha$ = 90°. |
| | b = 14.4350(2) Å | $\beta$ = 90°. |
| | c = 14.9930(2) Å | $\gamma$ = 90°. |
| Volume | 2333.92(5) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.194 $Mg/m^3$ | |
| Absorption coefficient | 0.077 $mm^{-1}$ | |
| F(000) | 904 | |
| Crystal size | 0.50 × 0.25 × 0.13 $mm^3$ | |
| Theta range for data collection | 2.72 to 27.47°. | |
| Index ranges | -13<=h<=13, -18<=k<=18, -19<=l<=19 | |
| Reflections collected | 48955 | |
| Independent reflections | 5320 [R(int) = 0.0578] | |
| Completeness to theta = 27.47° | 99.6 % | |
| Absorption correction | None | |
| Max. and min. transmission | 0.9901 and 0.9626 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 5320 / 0 / 286 | |
| Goodness-of-fit on F2 | 1.073 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0327, wR2 = 0.0794 | |
| R indices (all data) | R1 = 0.0361, wR2 = 0.0822 | |
| Absolute structure parameter | 0.0(7) | |
| Extinction coefficient | 0.017(2) | |
| Largest diff. peak and hole | 0.143 and -0.162 e.$Å^{-3}$ | |

**Table 12** *Atomic coordinates (× $10^4$) and equivalent isotropic displacement parameters ($Å^2$ × $10^3$) for (R)-**299***

| | x | y | z | U(eq)[a] |
|---|---|---|---|---|
| N(1) | 10071(1) | 1790(1) | 2562(1) | 25(1) |
| O(1) | 12275(1) | 1972(1) | 4309(1) | 38(1) |
| O(2) | 11103(1) | 4043(1) | 4086(1) | 39(1) |
| O(3) | 6273(1) | 1694(1) | 2945(1) | 45(1) |
| C(1) | 11016(1) | 1132(1) | 2907(1) | 24(1) |
| C(2) | 10157(1) | 2694(1) | 3008(1) | 27(1) |
| C(3) | 8794(1) | 1453(1) | 2616(1) | 28(1) |
| C(4) | 11183(1) | 285(1) | 2290(1) | 28(1) |
| C(5) | 12280(1) | -299(1) | 2620(1) | 34(1) |
| C(6) | 11386(1) | 580(1) | 1326(1) | 40(1) |
| C(11) | 11455(1) | 1296(1) | 4566(1) | 34(1) |
| C(12) | 10813(1) | 844(1) | 3877(1) | 29(1) |
| C(13) | 10019(1) | 121(1) | 4107(1) | 36(1) |
| C(14) | 9863(1) | -153(1) | 4993(1) | 49(1) |
| C(15) | 10481(1) | 319(1) | 5655(1) | 56(1) |
| C(16) | 11270(1) | 1045(1) | 5450(1) | 48(1) |
| C(17) | 12949(2) | 2447(1) | 4987(1) | 53(1) |
| C(21) | 11743(1) | 3934(1) | 3302(1) | 32(1) |
| C(22) | 11276(1) | 3251(1) | 2727(1) | 28(1) |
| C(23) | 11839(1) | 3135(1) | 1902(1) | 31(1) |
| C(24) | 12856(1) | 3670(1) | 1649(1) | 37(1) |
| C(25) | 13320(1) | 4322(1) | 2232(1) | 42(1) |
| C(26) | 12770(1) | 4457(1) | 3057(1) | 39(1) |
| C(27) | 11529(2) | 4734(1) | 4697(1) | 51(1) |
| C(31) | 6675(1) | 2053(1) | 2149(1) | 35(1) |
| C(32) | 7946(1) | 1965(1) | 1970(1) | 29(1) |
| C(33) | 8396(1) | 2341(1) | 1180(1) | 36(1) |
| C(34) | 7622(2) | 2784(1) | 573(1) | 46(1) |
| C(35) | 6374(2) | 2852(1) | 757(1) | 51(1) |
| C(36) | 5896(1) | 2490(1) | 1538(1) | 48(1) |
| C(37) | 4996(1) | 1816(1) | 3166(1) | 62(1) |

[a] U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

**Table 13** *Bond Lengths for (R)-**299***

| Bond | Length /Å | Bond | Length /Å |
|---|---|---|---|
| N(1)-C(3) | 1.4626(14) | C(22)-C(23) | 1.3877(16) |
| N(1)-C(2) | 1.4678(13) | C(23)-C(24) | 1.3939(17) |
| N(1)-C(1) | 1.4867(13) | C(23)-H(23) | 0.9500 |
| O(1)-C(11) | 1.3724(16) | C(24)-C(25) | 1.3784(19) |
| O(1)-C(17) | 1.4237(15) | C(24)-H(24) | 0.9500 |
| O(2)-C(21) | 1.3714(15) | C(25)-C(26) | 1.386(2) |
| O(2)-C(27) | 1.4301(15) | C(25)-H(25) | 0.9500 |
| O(3)-C(31) | 1.3717(16) | C(26)-H(26) | 0.9500 |
| O(3)-C(37) | 1.4278(16) | C(27)-H(27A) | 0.9800 |
| C(1)-C(12) | 1.5271(15) | C(27)-H(27B) | 0.9800 |
| C(1)-C(4) | 1.5439(14) | C(27)-H(27C) | 0.9800 |
| C(1)-H(1) | 1.0000 | C(31)-C(36) | 1.3942(18) |
| C(2)-C(22) | 1.5108(16) | C(31)-C(32) | 1.4023(17) |
| C(2)-H(2A) | 0.9900 | C(32)-C(33) | 1.3895(18) |
| C(2)-H(2B) | 0.9900 | C(33)-C(34) | 1.3906(18) |
| C(3)-C(32) | 1.5235(15) | C(33)-H(33) | 0.9500 |
| C(3)-H(3A) | 0.9900 | C(34)-C(35) | 1.377(2) |
| C(3)-H(3B) | 0.9900 | C(34)-H(34) | 0.9500 |
| C(4)-C(6) | 1.5234(16) | C(35)-C(36) | 1.382(2) |
| C(4)-C(5) | 1.5346(15) | C(35)-H(35) | 0.9500 |
| C(4)-H(4) | 1.0000 | C(36)-H(36) | 0.9500 |
| C(5)-H(5A) | 0.9800 | C(37)-H(37A) | 0.9800 |
| C(5)-H(5B) | 0.9800 | C(37)-H(37B) | 0.9800 |
| C(5)-H(5C) | 0.9800 | C(37)-H(37C) | 0.9800 |
| C(6)-H(6A) | 0.9800 | C(3)-N(1)-C(2) | 109.30(8) |
| C(6)-H(6B) | 0.9800 | C(3)-N(1)-C(1) | 114.38(8) |
| C(6)-H(6C) | 0.9800 | C(2)-N(1)-C(1) | 111.51(8) |
| C(11)-C(16) | 1.3893(17) | C(11)-O(1)-C(17) | 118.10(11) |
| C(11)-C(12) | 1.4041(17) | C(21)-O(2)-C(27) | 117.85(11) |
| C(12)-C(13) | 1.3937(17) | C(31)-O(3)-C(37) | 117.38(12) |
| C(13)-C(14) | 1.3956(18) | N(1)-C(1)-C(12) | 114.00(8) |
| C(13)-H(13) | 0.9500 | N(1)-C(1)-C(4) | 112.19(8) |
| C(14)-C(15) | 1.377(2) | C(12)-C(1)-C(4) | 111.87(9) |
| C(14)-H(14) | 0.9500 | N(1)-C(1)-H(1) | 106.0 |
| C(15)-C(16) | 1.384(2) | C(12)-C(1)-H(1) | 106.0 |
| C(15)-H(15) | 0.9500 | C(4)-C(1)-H(1) | 106.0 |
| C(16)-H(16) | 0.9500 | N(1)-C(2)-C(22) | 113.38(9) |
| C(17)-H(17A) | 0.9800 | N(1)-C(2)-H(2A) | 108.9 |
| C(17)-H(17B) | 0.9800 | C(22)-C(2)-H(2A) | 108.9 |
| C(17)-H(17C) | 0.9800 | N(1)-C(2)-H(2B) | 108.9 |
| C(21)-C(26) | 1.3902(18) | C(22)-C(2)-H(2B) | 108.9 |
| C(21)-C(22) | 1.4033(16) | H(2A)-C(2)-H(2B) | 107.7 |

**Table 14** *Bond Angles for (R)-**299***

| Bond | Angle /° | Bond | Angle /° |
|---|---|---|---|
| N(1)-C(3)-C(32) | 111.63(9) | O(2)-C(21)-C(26) | 124.41(11) |
| N(1)-C(3)-H(3A) | 109.3 | O(2)-C(21)-C(22) | 115.24(10) |
| C(32)-C(3)-H(3A) | 109.3 | H(37B)-C(37)-H(37C) | 109.5 |
| N(1)-C(3)-H(3B) | 109.3 | O(1)-C(17)-H(17B) | 109.5 |
| H(3A)-C(3)-H(3B) | 108.0 | H(17A)-C(17)-H(17B) | 109.5 |
| C(6)-C(4)-C(5) | 110.39(9) | O(1)-C(17)-H(17C) | 109.5 |
| C(6)-C(4)-C(1) | 111.35(9) | H(17A)-C(17)-H(17C) | 109.5 |
| C(5)-C(4)-C(1) | 109.35(9) | H(17B)-C(17)-H(17C) | 109.5 |
| C(6)-C(4)-H(4) | 108.6 | C(26)-C(21)-C(22) | 120.35(12) |
| C(5)-C(4)-H(4) | 108.6 | C(23)-C(22)-C(21) | 118.41(11) |
| C(1)-C(4)-H(4) | 108.6 | C(23)-C(22)-C(2) | 122.24(10) |
| C(4)-C(5)-H(5A) | 109.5 | C(21)-C(22)-C(2) | 119.31(10) |
| C(4)-C(5)-H(5B) | 109.5 | C(22)-C(23)-C(24) | 121.32(11) |
| H(5A)-C(5)-H(5B) | 109.5 | C(22)-C(23)-H(23) | 119.3 |
| C(4)-C(5)-H(5C) | 109.5 | C(24)-C(23)-H(23) | 119.3 |
| H(5A)-C(5)-H(5C) | 109.5 | C(25)-C(24)-C(23) | 119.43(12) |
| H(5B)-C(5)-H(5C) | 109.5 | C(25)-C(24)-H(24) | 120.3 |
| C(4)-C(6)-H(6A) | 109.5 | C(23)-C(24)-H(24) | 120.3 |
| C(4)-C(6)-H(6B) | 109.5 | C(24)-C(25)-C(26) | 120.45(12) |
| H(6A)-C(6)-H(6B) | 109.5 | C(24)-C(25)-H(25) | 119.8 |
| C(4)-C(6)-H(6C) | 109.5 | C(26)-C(25)-H(25) | 119.8 |
| H(6A)-C(6)-H(6C) | 109.5 | C(25)-C(26)-C(21) | 120.01(12) |
| H(6B)-C(6)-H(6C) | 109.5 | C(25)-C(26)-H(26) | 120.0 |
| O(1)-C(11)-C(16) | 123.07(12) | C(21)-C(26)-H(26) | 120.0 |
| O(1)-C(11)-C(12) | 116.23(10) | O(2)-C(27)-H(27A) | 109.5 |
| C(16)-C(11)-C(12) | 120.69(13) | O(2)-C(27)-H(27B) | 109.5 |
| C(13)-C(12)-C(11) | 117.93(11) | H(27A)-C(27)-H(27B) | 109.5 |
| C(13)-C(12)-C(1) | 121.82(10) | O(2)-C(27)-H(27C) | 109.5 |
| C(11)-C(12)-C(1) | 120.23(10) | H(27A)-C(27)-H(27C) | 109.5 |
| C(12)-C(13)-C(14) | 121.48(13) | H(27B)-C(27)-H(27C) | 109.5 |
| C(12)-C(13)-H(13) | 119.3 | O(3)-C(31)-C(36) | 123.54(12) |
| C(14)-C(13)-H(13) | 119.3 | O(3)-C(31)-C(32) | 116.17(10) |
| C(15)-C(14)-C(13) | 119.19(13) | C(36)-C(31)-C(32) | 120.29(13) |
| C(15)-C(14)-H(14) | 120.4 | C(33)-C(32)-C(31) | 117.95(11) |
| C(13)-C(14)-H(14) | 120.4 | C(33)-C(32)-C(3) | 121.43(10) |
| C(14)-C(15)-C(16) | 120.80(12) | C(31)-C(32)-C(3) | 120.61(11) |
| C(14)-C(15)-H(15) | 119.6 | C(32)-C(33)-C(34) | 121.86(13) |
| C(16)-C(15)-H(15) | 119.6 | C(32)-C(33)-H(33) | 119.1 |
| C(15)-C(16)-C(11) | 119.85(14) | C(34)-C(33)-H(33) | 119.1 |
| C(15)-C(16)-H(16) | 120.1 | C(35)-C(34)-C(33) | 119.24(14) |
| C(11)-C(16)-H(16) | 120.1 | C(35)-C(34)-H(34) | 120.4 |
| O(1)-C(17)-H(17A) | 109.5 | C(33)-C(34)-H(34) | 120.4 |

**Table 14** *(cont)*

| Bond | Angle /° | Bond | Angle /° |
|---|---|---|---|
| C(34)-C(35)-C(36) | 120.44(13) | O(3)-C(37)-H(37A) | 109.5 |
| C(34)-C(35)-H(35) | 119.8 | O(3)-C(37)-H(37B) | 109.5 |
| C(36)-C(35)-H(35) | 119.8 | H(37A)-C(37)-H(37B) | 109.5 |
| C(35)-C(36)-C(31) | 120.21(13) | O(3)-C(37)-H(37C) | 109.5 |
| C(35)-C(36)-H(36) | 119.9 | H(37A)-C(37)-H(37C) | 109.5 |
| C(31)-C(36)-H(36) | 119.9 | | |

**Table 15** *Anisotropic displacement parameters ($Å^2$ × 103) for (R)-**293**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\,h\,k\,a^*\,b^*\,U^{12}]$*

| | U11 | U22 | U33 | U23 | U13 | U12 |
|---|---|---|---|---|---|---|
| N(1) | 23(1) | 25(1) | 26(1) | -1(1) | -2(1) | 2(1) |
| O(1) | 35(1) | 48(1) | 32(1) | -4(1) | -10(1) | -2(1) |
| O(2) | 42(1) | 38(1) | 38(1) | -12(1) | -2(1) | -4(1) |
| O(3) | 26(1) | 47(1) | 63(1) | 6(1) | 5(1) | 5(1) |
| C(1) | 22(1) | 26(1) | 24(1) | 1(1) | 0(1) | 3(1) |
| C(2) | 26(1) | 28(1) | 28(1) | -4(1) | -1(1) | 3(1) |
| C(3) | 23(1) | 31(1) | 30(1) | 0(1) | -1(1) | 1(1) |
| C(4) | 28(1) | 28(1) | 30(1) | -2(1) | 2(1) | 2(1) |
| C(5) | 37(1) | 31(1) | 36(1) | 3(1) | 4(1) | 8(1) |
| C(6) | 50(1) | 40(1) | 28(1) | -4(1) | 2(1) | 14(1) |
| C(11) | 27(1) | 47(1) | 28(1) | 2(1) | -1(1) | 11(1) |
| C(12) | 26(1) | 35(1) | 27(1) | 3(1) | 2(1) | 8(1) |
| C(13) | 30(1) | 41(1) | 38(1) | 8(1) | 5(1) | 5(1) |
| C(14) | 34(1) | 64(1) | 48(1) | 25(1) | 12(1) | 8(1) |
| C(15) | 37(1) | 98(1) | 31(1) | 24(1) | 6(1) | 16(1) |
| C(16) | 37(1) | 82(1) | 26(1) | 5(1) | -4(1) | 14(1) |
| C(17) | 47(1) | 70(1) | 42(1) | -14(1) | -17(1) | -1(1) |
| C(21) | 31(1) | 29(1) | 36(1) | 0(1) | -5(1) | 3(1) |
| C(22) | 27(1) | 24(1) | 33(1) | 1(1) | -4(1) | 4(1) |
| C(23) | 32(1) | 28(1) | 34(1) | 3(1) | -2(1) | 3(1) |
| C(24) | 34(1) | 35(1) | 41(1) | 9(1) | 3(1) | 5(1) |
| C(25) | 32(1) | 35(1) | 58(1) | 10(1) | 0(1) | -3(1) |
| C(26) | 36(1) | 31(1) | 50(1) | -1(1) | -10(1) | -3(1) |
| C(27) | 62(1) | 45(1) | 46(1) | -16(1) | -6(1) | -9(1) |
| C(31) | 32(1) | 29(1) | 44(1) | -6(1) | -6(1) | 2(1) |
| C(32) | 28(1) | 27(1) | 32(1) | -7(1) | -7(1) | 4(1) |
| C(33) | 40(1) | 39(1) | 30(1) | -4(1) | -6(1) | 8(1) |
| C(34) | 56(1) | 48(1) | 35(1) | -1(1) | -12(1) | 11(1) |
| C(35) | 52(1) | 53(1) | 48(1) | -2(1) | -24(1) | 14(1) |
| C(36) | 32(1) | 46(1) | 65(1) | -8(1) | -17(1) | 8(1) |
| C(37) | 28(1) | 64(1) | 95(1) | 9(1) | 13(1) | 6(1) |

# APPENDIX 3:
# *Publications*

COMMUNICATION

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# Synthesis, structure and catalytic activity of an air-stable titanium triflate, supported by an amine tris(phenolate) ligand†

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**An air- and moisture-stable titanium(IV) triflate, 3, supported by a $C_3$-symmetric amine tris(phenolate) ligand has been synthesised, characterised by X-ray crystallography and demonstrated to be an excellent catalyst for formal aza-Diels–Alder reactions.**

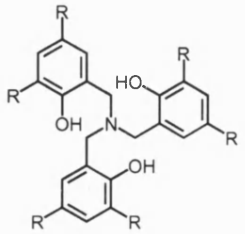
Titanium(IV) compounds, which are usually derived from halide, alkoxide, phenolate or triflate ligands, are amongst the most widely used catalysts in organic synthesis.[1] Although these salts (or their precursors) are often cheap and commercially available, they have the disadvantage of being air- and moisture-sensitive liquids requiring storage and manipulation under inert conditions. Furthermore, in significant quantities, they can present a considerable caustic and corrosive hazard.[2] Therefore, the design of new titanium-based reagents that are convenient to use yet retain high catalytic activity is of considerable importance to the synthetic community. In this communication we describe the development of air-stable titanium complexes of an easily prepared amine tris(phenolate) ligand and report the remarkable reactivity of the air-stable triflate salt **3** as a catalyst for formal aza-Diels–Alder reactions.[3]

In common with a wide range of other tripodal ligands, there has been much recent interest in main group and transition metal coordination chemistry of amine tris(phenolate) ligands derived from **1a–c** (where R = Me, **1a**; $^t$Bu, **1b**; H, **1c**).[4,5] Given the ease of preparation of these ligands *via* a one-pot variant of the Mannich reaction, its unusual yet simple coordination chemistry, and the reported activity of similar titanium complexes as polymerisation catalysts,[5] we considered that titanium complexes of **1a–c** might be versatile catalysts in organic synthesis.

The amine tris(phenolate) titanium isopropoxide **2a** was prepared in high yield from **1a** using a modification of the procedure reported by Kol *et al.*[5c] Its identity was established spectroscopically,† and was confirmed by a single crystal X-ray structure ‡ (Fig. 1) which revealed a monomeric, $C_3$-symmetric complex as expected. The approximately trigonal bipyramidal Ti centre lies slightly above the plane of the three equatorial phenolate oxygen atoms whilst the axial sites are occupied by the neutral nitrogen atom of the ligand, and the monodentate isopropoxide anion. The complex **2a**, although generated from an achiral ligand is racemic, since complexation to the metal centre results in the formation of two enantiomers with 'propeller' chirality. This was evidenced by the presence of both *P* and *M* enantiomers in the crystallographic asymmetric unit, whilst two resonances at $\delta$ 2.75 and 3.89, ($J$ = 10.6 Hz) were observed in the $^1$H NMR spectrum of **2a** that were ascribed to the diastereotopic $N$–$CH_2$ protons of the tripodal ligand fragment. The structural parameters of **2a** are very similar to those reported previously for the related amine tris(phenolate) titanium isopropoxide **2b** derived from **1b**.[5c]

In preliminary screening experiments for catalytic activity, we found complex **2a** to be a poor Lewis acid catalyst for a range of synthetic transformations for which Lewis acidic titanium alkoxides and phenolates have been used previously. We reasoned that this lack of reactivity was in part due to stabilisation of the metal centre arising from apical *N* donation from the amine tris(phenolate) ligand, and that an alternative complex containing a more weakly coordinating apical ligand would enhance catalyst reactivity.

Reaction of **2a** with $Me_3SiOTf$ yielded complex **3** in high yield† whose structure was determined by X-ray crystallography (Fig. 2).‡ As expected, the triflate bond to Ti in **3** was significantly longer than the equivalent parameter in the alkoxide **2a** [Ti–O distances: 1.774(2)/1.776(2) Å for alkoxide **2a** *vs.* 2.002(2)/2.017(2) Å for triflate **3**] suggesting weaker metal–ligand coordination. There is a concomitant shortening




**1a-c**

**1a** R=Me; **1b** R=$^t$Bu; **1c** R=H

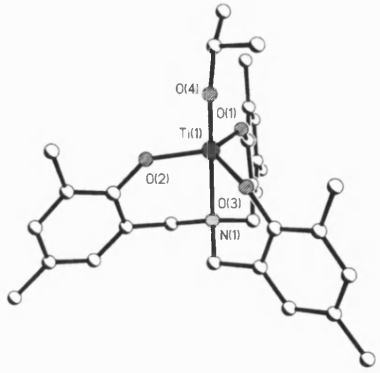



**Fig. 1** Molecular structure of **2a** (only one of two similar molecules found within the asymmetric unit shown and hydrogen atoms omitted for clarity). Selected bond lengths (Å): Ti(1)–O(1) 1.862(2), Ti(1)–O(2) 1.845(2), Ti(1)–O(3) 1.851(2), Ti(1)–O(4) 1.774(2), Ti(1)–N(1) 2.305(2); Bond angles (°): N(1)–Ti(1)–O(4) 179.70(8), Ti(1)–O(1)–C(11) 141.71(15), Ti(1)–O(2)–C(21) 143.19(15), Ti(1)–O(3)–C(31) 141.87(14), Ti(1)–O(4)–C(41) 161.56(18).

† Electronic supplementary information (ESI) available: characterisation data and experimental procedures for the synthesis of **2a** and **3** and experimental details of aza-Diels–Alder reactions using **3** as a catalyst. See http://www.rsc.org/suppdata/cc/b3/b304704k/

DOI: 10.1039/b304704k

(and implied strengthening) of the Ti–N bond in triflate **3** [Ti–N distances: 2.303(2)/2.295(2) Å for **2a** and 2.216(2)/2.213(2) Å for **3**, respectively]; a slight shortening of the Ti–O(phenolate) distances [average Ti–O(phenolate) distance: 1.850 for **2a** and 1.797 Å for **3**]; whilst the Ti atom sits further into the 'pocket' of the ligand for **2a** [distance of Ti atom above the plane of the three phenolate O atoms: 0.251(1)/0.247(1) Å for **2a** and 0.188(1)/0.178(1) Å for **3**]. There is little variation in the tilt of the propeller between the two complexes (average angle between aryl planes and Ti–N bond vector: 15.2° for **2a** and 13.0° for **3**).

In catalytic screening triflate **3** demonstrated significantly enhanced activity relative to the isopropoxide complex **2a**.[6] We chose to optimise the use of **3** as a catalyst for the formal aza-Diels–Alder reaction between imine **4a** and Danishefsky's diene **5** (Scheme 1), since this reaction was known not to occur in $CH_2Cl_2$ in the absence of a strong Lewis acid.[7] Our results demonstrate that triflate **3** is competitive with the best-known catalysts available for this reaction.[8] For example, 10 mol% of catalyst **3** resulted in 100% conversion of imine **4a** and diene **5** to *N*-benzyl-2,3-dihydro-2-phenyl-1*H*-pyridin-4-one **6a** (73% isolated yield) at room temperature in 45 minutes. Subsequent use of 10 mol% of triflate **3** as a catalyst for a representative range of *N*-benzyl-imines **4b–f** with diene **5** afforded the corresponding 2,3-dihydropyridin-4-ones **6b–f** in good yield (56–73%),[9] with reaction times of < 1.5 h in all cases (Scheme 1, Table 1).

The observed catalytic activity of triflate **3** is notable in itself, however most importantly, and in marked contrast to other titanium-based reagents in common usage, **3** is an air- and moisture-stable crystalline solid that is simple to prepare and isolate on a reasonable scale. For example, in the course of this work we have used one batch of **3** on the bench over a period of three months with no noticeable loss in activity or degradation.

In summary, we have described the use of $C_3$-symmetric titanium triphenolate **3** as a catalyst for formal aza-Diels–Alder reactions. In addition to being a cheap and readily prepared complex, **3** is an air-stable crystalline solid making it a very attractive reagent for use as a Lewis acid catalyst in synthetic laboratories. We are currently investigating further the range of synthetic transformations in which triflates **3** can function as an effective catalyst.

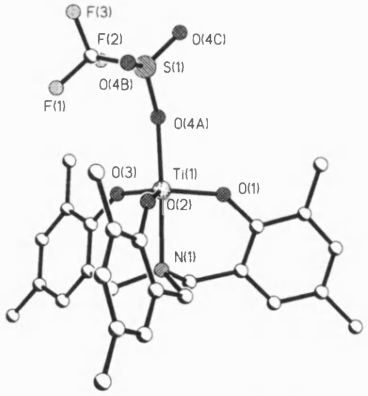
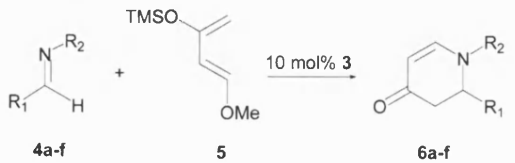



**Fig. 2** Molecular structure of **3** (only one of two similar molecules found within the asymmetric unit shown and hydrogen atoms omitted for clarity). Selected bond lengths (Å): Ti(1)–O(1) 1.793(2), Ti(1)–O(2) 1.799(2), Ti(1)–O(3) 1.808(2), Ti(1)–O(4A) 2.002(2), Ti(1)–N(1) 2.216(2); Bond angles (°): N(1)–Ti(1)–O(4A) 177.25(8), Ti(1)–O(1)–C(11) 141.94(17), Ti(1)–O(2)–C(21) 143.15(16), Ti(1)–O(3)–C(31) 142.62(16), Ti(1)–O(4A)–S(1) 158.14(12).




**Scheme 1**

**Table 1** Yield of dihydropyridin-4-ones **6a–f**

| Entry | $R_1$ | $R_2$ | Time/min | Yield[a] (%) |
|---|---|---|---|---|
| a | Ph | Bn | 45 | 73 |
| b | 2-Npth | Bn | 40 | 71 |
| c | 3,5-$(MeO)_2$Ph | Bn | 70 | 60 |
| d | Cyc | Bn | 45 | 56 |
| e | Ph | $^i$Pr | 60 | 72 |
| f | Ph | 3,4-$(MeO)_2$Bn | 80 | 62 |

[a] All yields for chromatographically pure compounds. $^1$H NMR spectroscopic analysis of crude reaction products revealed that **6a–f** were formed in 100% conversion as the only products.

We thank the EPSRC (M. G. D., D. E. J. E. R.), the Royal Society (S. B. D., M. G. D.) and the University of Bath (A. L. J.).

## Notes and references

‡ *Crystallography*. Data were collected on a Nonius KappaCCD area detector diffractometer using Mo-Kα radiation ($\lambda$ = 0.71073 Å), and all structures were solved by direct methods and refined on all $F^2$ data using the SHELX-97 suite of programs.[10]

Crystal data for **2a**: $C_{30}H_{37}N_1O_4Ti_1$, $M$ = 523.51, yellow blocks, crystal size 0.25 × 0.22 × 0.17 mm, triclinic, $P\bar{1}$, $a$ = 13.0760(1), $b$ = 14.2000(2), $c$ = 16.4720(3) Å, $\alpha$ = 82.170(1), $\beta$ = 88.758(1), $\gamma$ = 62.785(1)°, $V$ = 2691.70(7) Å$^3$, $Z$ = 4, $D_c$ = 1.292 g cm$^{-3}$, $T$ = 150(2) K, 52968 reflections measured, 12285 unique reflections ($2\theta$ = 27.51°, $R_{int}$ = 0.0556) against 666 parameters gave $R_1$ = 0.0500 and $wR_2$ = 0.1181 [$I > 2\sigma(I)$] ($R_1$ = 0.0803 and $wR2$ = 0.1306 for all data). CCDC 209584.

For **3**: $C_{59.5}H_{64}F_6N_2O_3S_2Ti_2$, $M$ = 1273.04, red blocks, crystal size 0.20 × 0.22 × 0.15 mm, triclinic, $P\bar{1}$, $a$ = 10.1340(2), $b$ = 16.8420(3), $c$ = 18.2010(4) Å, $\alpha$ = 101.613(1), $\beta$ = 93.762(1), $\gamma$ = 95.259(1)°, $V$ = 3018.8(1) Å$^3$, $Z$ = 2, $D_c$ = 1.401 g cm$^{-3}$, $T$ = 150(2) K, 41484 reflections measured, 10600 unique reflections ($2\theta$ = 25.03°, $R_{int}$ = 0.0420) against 786 parameters gave $R_1$ = 0.0436 and $wR2$ = 0.1056 [$I > 2\sigma(I)$] ($R_1$ = 0.0630 and $wR2$ = 0.1159 for all data). CCDC 209585. See http://www.rsc.org/suppdata/cc/b3/b304704k/ for crystallographic data in CIF or other electronic format.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# Kinetic resolution strategies using non-enzymatic catalysts

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**Abstract**—Recent advances in the use of non-enzymatic chiral catalysts for the kinetic resolution or dynamic kinetic resolution of racemic substrates are described. Successful protocols that afford recovered starting material or products in high enantiomeric excess are included, and mechanistic detail is discussed where appropriate. Relevant examples illustrate the wide range of different reaction scenarios where kinetic resolution has recently been employed as a strategy for the efficient synthesis of enantiopure compounds. 

**Contents**



## 1. Introduction

The development of low molecular weight chiral catalysts for asymmetric synthesis has been one of the major breakthroughs in organic synthesis over the last 30 years. Within this context, a significant number of enantioselective catalysts are now available that afford excellent levels of stereocontrol that could only previously be achieved using biocatalysts. Whilst the use of enzymes for the kinetic resolution of racemic substrates to afford enantiopure compounds in high e.e. and good yields has emerged as a popular strategy in synthesis,[1] it is only relatively recently that the widespread application of non-enzymatic chiral catalysts for kinetic resolution[2] (or dynamic kinetic resolution[3]) has gained popularity within the synthetic community. Major developments using non-enzymatic catalysts for kinetic resolution prior to 2000 have been extensively reported,[4] and consequently it is the intention of this review to document comprehensively major developments within this fast moving area over the last three years.[5] No attempts have been made to discuss the fundamental principles associated with kinetic resolution strategies, since these concepts have been dealt with in great detail elsewhere.[6] We have confined ourselves to those reports that employ sub-stoichiometric amounts of catalyst or chiral ligand for kinetic resolution, and consequently do not include those protocols that require stoichiometric quantities of chiral ligand or chiral reagent for stereocontrol.[7] Neither, do we discuss recent developments in chemo-enzymatic strategies that employ biocatalysts for enantioselective catalysis in the presence of metal-catalysed racemisation processes to afford elegant dynamic kinetic resolution protocols.[8] Since it is our intention to not only describe the range of enantioselective catalysts that have been applied for resolution, but also to provide a synthetic perspective on how widely this methodology has been adopted as a tool for the preparation of enantiopure compounds, we have

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0957-4166/03/$ - see front matter 
doi:10.1016/S0957-4166(03)00209-X

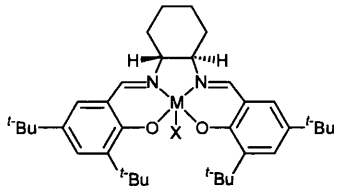



**Figure 1.** Salen complexes **1–4** used for HKR of terminal (*rac*)-epoxides.

concentrated primarily on reports that afford recovered starting materials or products in both high e.e. and in good yield.

## 2. Hydrolytic kinetic resolution of terminal racemic epoxides

Numerous reports have appeared over the last three years describing the use of Jacobsen's chiral (salen)–$Co^{III}$ or –$Cr^{III}$ complexes **1–4** (Fig. 1) for the stereoselective hydrolytic kinetic resolution (HKR) of terminal racemic epoxides.[9] HKR, using water as a nucleophile has been shown to be effective for the resolution of a wide range of racemic terminal epoxides, often affording both epoxides and their corresponding 1,2-diols in very high e.e. For example, HKR of racemic propylene oxide in the presence of 0.55 equiv. of water using only 0.2 mol% of salen catalyst (*R,R*)-**1**, affords recovered (*R*)-epoxide in >99% e.e. and in 46% yield (maximum 50%) after 18 h.[9] This approach has been applied to the kinetic resolution of a wide range of alkyl-, halo alkyl-, aryl-, vinyl- and alkynyl-racemic epoxides,[9] and has recently been extended to epoxides containing ω-sulfone,[10] and ω-diethyl phosphonate[11] functionalities, all of which afforded chiral epoxides in ≥93% e.e. (Fig. 2).

Unsurprisingly, the generality and broad substrate specificity of HKR has been exploited for the production of a wide range of chiral synthons for natural product synthesis, including recent strategies directed towards the synthesis of Epothilone A,[12] Laulimalide,[13] Fostriecin[14], Arachadonic acid metabolites,[15] (–)-Pyrenophorin,[16] Carquinostatin A[17] Bryostatins,[18] Ulapualide,[19] (–)-Mycalolide,[20] α,α-difluoroalkylphosphonate analogues of (Lyso)phosphatidic acid[21] and bicyclic lactones from parasitic wasps.[22] HKR has also been used for the production of a homochiral epoxide for the enantioselective synthesis of a chiral pyrrolidin-2-one for the treatment of hypertension and arrhythmia.[23] The use and range of chiral epoxides resolved in these natural product syntheses clearly stands as testament to the true power of HKR as *routine* methodology for stereoselective organic synthesis (Fig. 3).

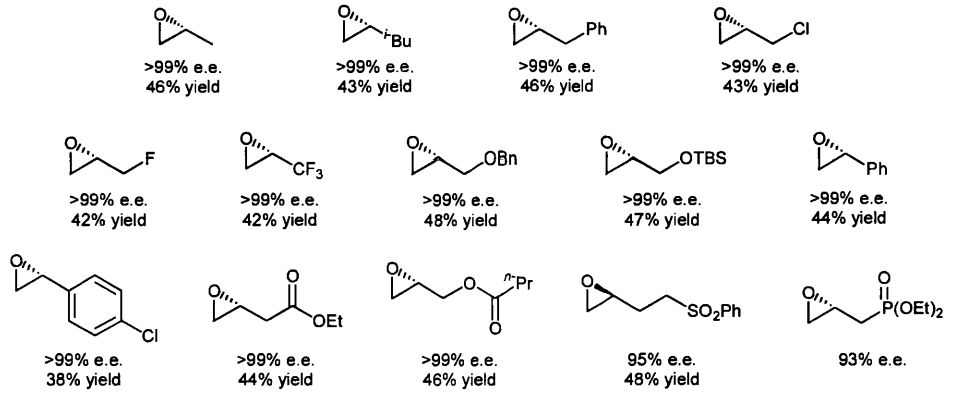



**Figure 2.** A representative range of (*rac*)-epoxides resolved using salen complexes (*R,R*)-**1** or (*S,S*)-**1**.

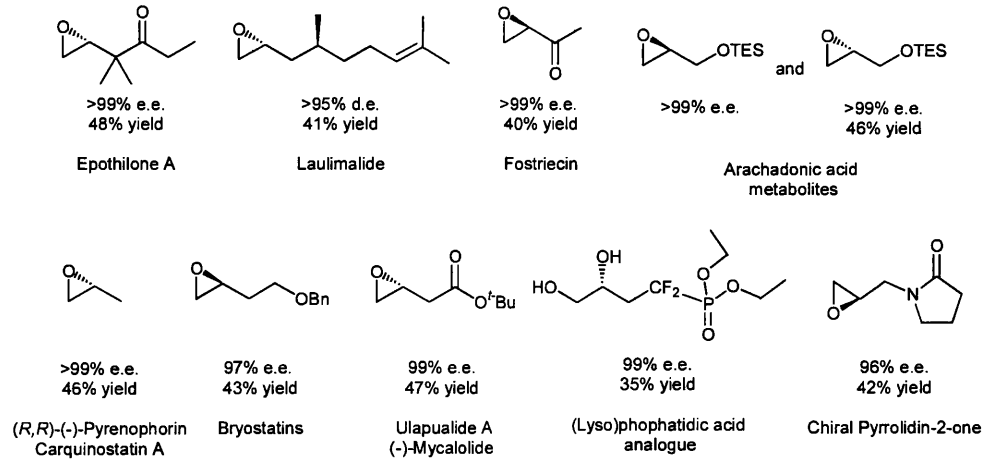


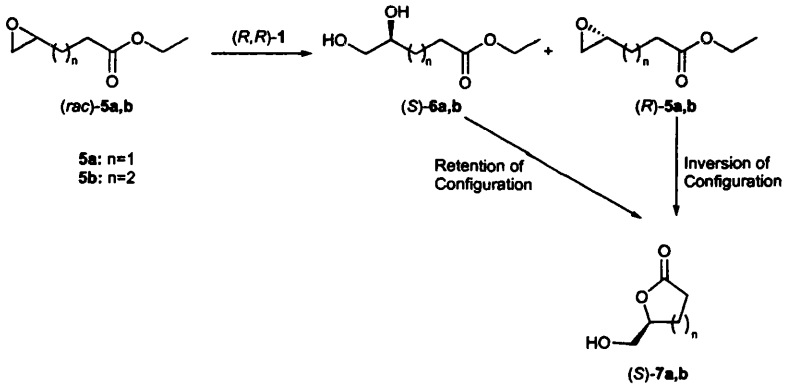

**Figure 3.** Range of chiral epoxides and diols resolved using HKR as synthons for natural product synthesis.

Liu et al. have demonstrated that judicious choice of substrate enables HKR to be compatible with enantioconvergent synthetic protocols in which both enantiomers of a racemic epoxide are converted to the same enantiopure product.[24] Thus, HKR of epoxide (*rac*)-**5a** under standard conditions afforded unreacted epoxide (*R*)-**5a** in 45% yield, and diol (*S*)-**6a** which cyclised in situ to afford δ-lactone (*S*)-**7a** in 94% e.e. and 50% yield. Subsequent treatment of recovered epoxide (*R*)-**5a** with aqueous TFA resulted in epoxide ring opening with inversion of configuration, followed by spontaneous cyclisation, to once again afford lactone (*S*)-**7a** in 96% e.e. and 44% yield (Scheme 1).

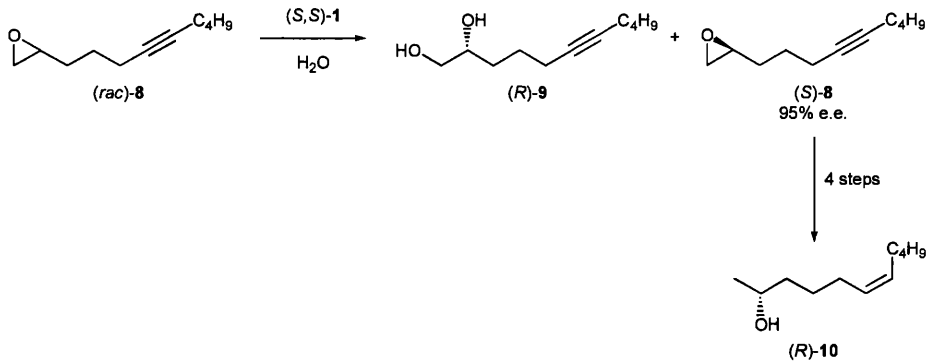
The HKR of mono- and bis-epoxides catalysed by catalyst (*S,S*)-**1** has also been used as the key step in the synthesis of a range of insect pheromones, demonstrating that structurally more complex racemic epoxides respond equally well to these procedures.[25] A representative example is the HKR of mono-epoxide (*rac*)-**8** for the synthesis of a pheromone of ant-lions, nostrenol (*R*)-**10**. The HKR of epoxide (*rac*)-**8** using (*S,S*)-**1** and 0.55 equiv. of $H_2O$ furnished (*S*)-**8** in 95% e.e. (and (*R*)-**9**) which was converted to nostrenol (*R*)-**10** over four steps (Scheme 2).

The HKR of a diastereoisomeric mixture of bis-epoxides containing (*meso*)-**11** and bis-epoxide (*rac*)-**12** with (*R,R*)-**1** and 0.8 equiv. of water produced bis-epoxide (*R,R*)-**12**, epoxydiol (2*R*,8*S*)-**13** and tetrol (*S,S*)-**14** in 24, 46 and 15% yields, respectively. This approach therefore employs catalyst (*R,R*)-**1** for the simultaneous enantioselective desymmetrisation of *meso*-**11** and the kinetic resolution of (*rac*)-**12**, thus affording useful quantities of epoxydiol (2*R*,8*S*)-**13** which was subsequently transformed into 1,7-dimethylnonyl propanoate (*R,R*)-**15** (the sex pheromone of the female western corn rootworm) in seven steps (Scheme 3).[26]

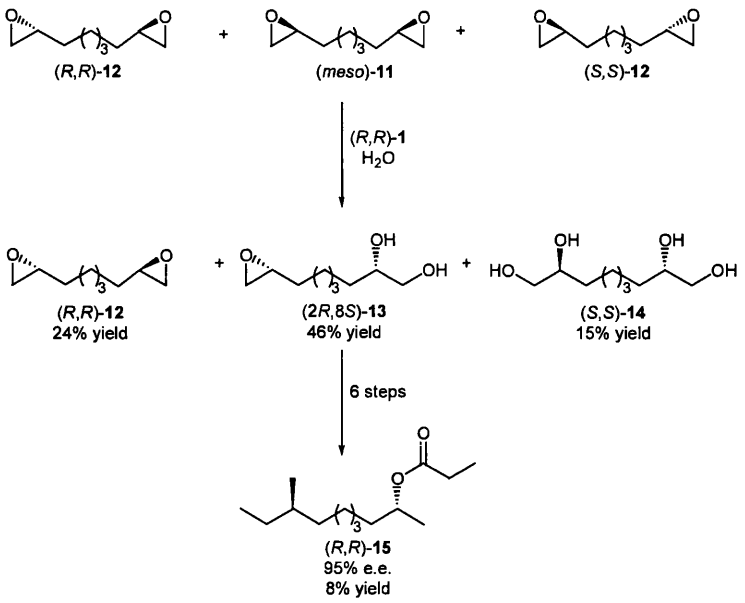
The potential of salen catalysts to 'resolve' mixtures of diastereoisomeric terminal epoxides (2*S*)-**16** and (2*R*)-**17** has been further demonstrated for the synthesis of diastereoisomers of aminohydroxyiminocarane (2*R*)-**19** and (2*S*)-**20** both of which exhibit localised anaesthetic activity. This approach involved treatment of diastereoisomeric epoxyiminocarene (2*S*)-**16** and (2*R*)-**17** with (salen)CoOAc (*R,R*)-**1** under standard HKR conditions to yield epoxide (2*R*)-**17** (>99% e.e.) and diol (2*S*)-**18** (>97% e.e.), respectively. Separation and subsequent synthetic manipulation of (2*R*)-**17** or (2*S*)-**18** using *iso*-propylamine as a nucleophile resulted in their stereoselective conversion into either




**Scheme 1.** Enantioconvergent transformation of (*rac*)-**5a,b** into γ- and δ-lactones (*S*)-**7a** and (*S*)-**7b** via HKR.




**Scheme 2.** Synthesis of nostrenol (*R*)-**10** via HKR.

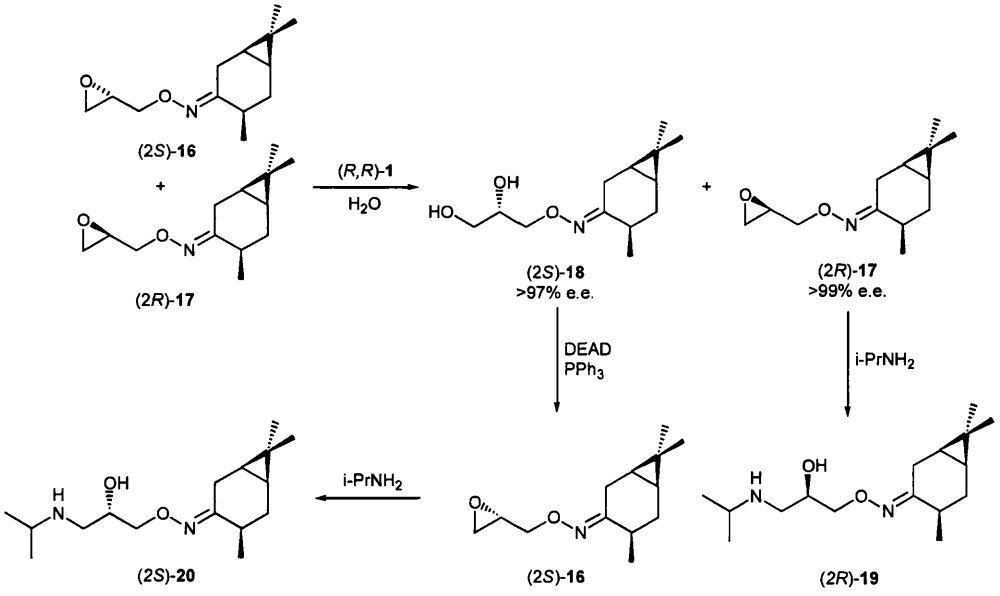



**Scheme 3.** Synthesis of the sex pheromone of the female western corn rootworm (*R*,*R*)-**15** via HKR.

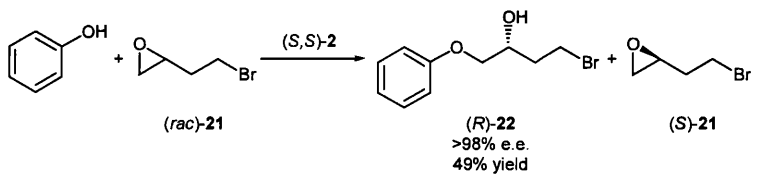
diastereoisomer of aminohydroxyiminocarane (2*R*)-**19** and (2*S*)-**20**, respectively (Scheme 4).[27]

Salen catalysts may also be employed for the ring opening of racemic epoxides using a variety of other nucleophiles, such as phenol, or azide.[28] For example, treatment of epoxide (*rac*)-**21** with 0.5 equiv. of phenol in the presence of catalyst (*S*,*S*)-**2** produced (*R*)-**22** in >98% e.e. in near quantitative yield (with respect to phenol), which was then used for the synthesis of a Prostaglandin $F_{1\alpha}$ analogue (Scheme 5).[29]

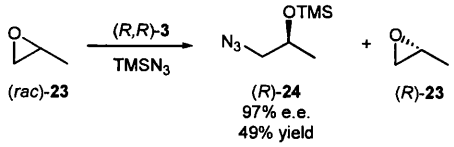
A representative example of the kinetic resolution of terminal racemic epoxides via enantioselective ring




**Scheme 4.** Synthesis of either diastereoisomer of aminohydroxyiminocarane (2*R*)-**19**/(2*S*)-**20** via HKR.




**Scheme 5.** Synthesis of Prostaglandin $F_{1\alpha}$ precursor (*R*)-**22** via HKR using phenol as a nucleophile.




**Scheme 6.** Kinetic resolution of propylene oxide (*rac*)-**23** with $TMSN_3$.

opening with $TMSN_3$ is described in Scheme 6, involving treatment of propylene oxide (*rac*)-**23** with 0.5 equiv. of $TMSN_3$ in the presence of (*R,R*)-**3** (1 mol%) which resulted in essentially quantitative conversion to a mixture of ring opened product (*R*)-**24** and epoxide (*R*)-**23** after 18 h at 0°C. The unreacted volatile epoxide was removed in vacuo leaving 1-azido-2-trimethyl-siloxypropane (*R*)-**24** in 97% e.e. and 49% yield. A representative range of ring-opened products that can be prepared in high e.e. using this variant of HKR methodology are shown in Fig. 4.[28] From a mechanistic perspective, it has been reported that HKR epoxide ring opening reactions using salen catalysts exhibit a second-order kinetic dependence on the catalyst, and that these resolutions also demonstrate non-linear effects when scalemic salen ligands are used for catalysis.[28,30] In order to explain these observations it has been proposed that one metal–salen complex acts as a Lewis acid to activate the epoxide towards ring opening, whilst another metal–salen complex serves to deliver the incipient nucleophile (Fig. 5). Consequently, it was proposed that catalysts derived from cyclic ligands that contained more than one metal centre in close proximity to each other might display enhanced reactivity relative to conventional monomeric salen catalyst systems. Thus, a range of oligomeric (salen)Co complexes **25** and **26** (Fig. 6) were prepared and shown to be highly effective catalysts for the asymmetric ring opening of epoxides, affording catalytic systems with higher enantioselectivities, and reactivities than those observed for monomeric catalyst (*R,R*)-**4** (Table 1). For example, cyclic oligosalen catalyst **25**, which exists as a complicated mixture of diastereoisomeric oligomers of varying ring size ($n=1$–5), was found to catalyse the HKR of various terminal epoxides (*rac*)-**28a–e** with a range of alcohols **27a–e** as nucleophiles to afford ring opened products **29a–e** in >98% e.e. and in 46–50% yield (Scheme 7).[31] Subsequent investigations revealed that a monomeric pimelate linked trimeric oligosalen complex **26** (X=csa, $n=2$) demonstrated even higher enantioselectivity and reactivity than those observed for the oligomeric mixture of cyclic salen catalysts **25**.[32]

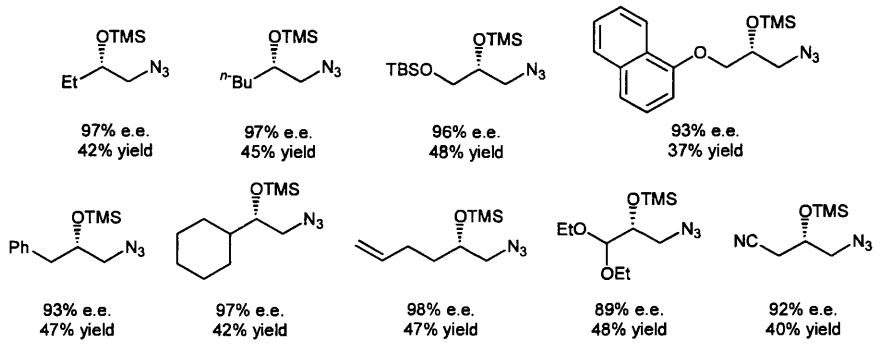



**Figure 4.** Synthons produced via HKR using $TMSN_3$ as a nucleophile.

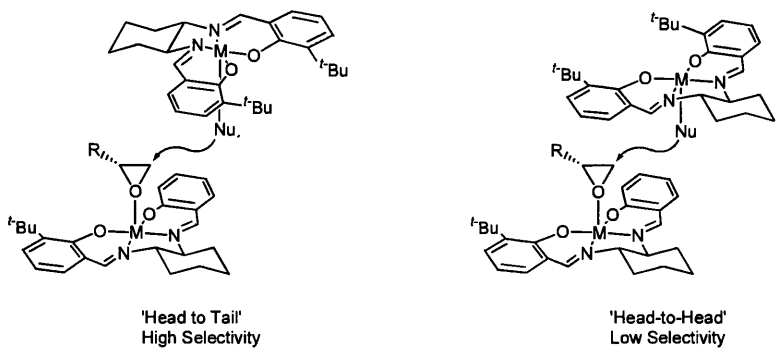
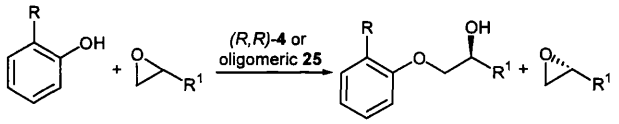
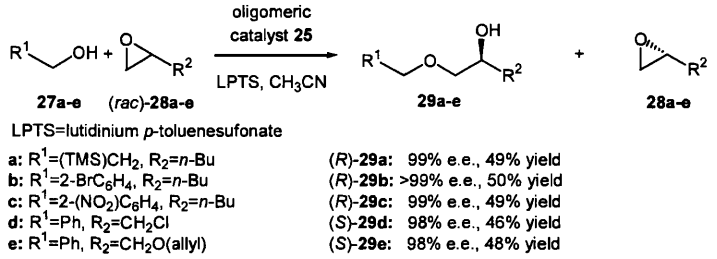



**Figure 5.** Competing transition states for epoxide ring-opening using salen catalysts.

**Table 1.** Kinetic resolution of racemic epoxides with phenol catalysed by (salen)Co complexes (*R*,*R*)-**4** or **25**




| R | $R^1$ | Catalyst | Co (mol%) | e.e. α-aryloxy-alcohol | % Yield α-aryloxy-alcohol |
|---|---|---|---|---|---|
| H | $CH_2Cl$ | (*R*,*R*)-**4** | 4.0 | 99 | 48 |
| | | **25** | 0.25 | 99 | 50 |
| H | *c*-Hexyl | (*R*,*R*)-**4** | 8.0 | 94 | 45 |
| | | **25** | 0.5 | 98 | 49 |
| Cl | $^n$Bu | (*R*,*R*)-**4** | 4.0 | 68 | 40 |
| | | **25** | 0.8 | 99 | 0.8 |




**Scheme 7.** Kinetic resolution of racemic epoxides with alcohols catalysed by oligomeric catalyst **25**.

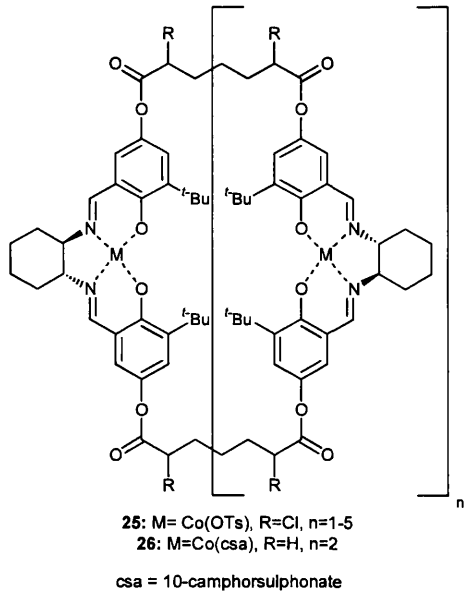
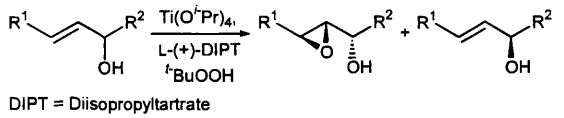



**Figure 6.** Oligomeric (salen)Co catalysts **25** and **26** for HKR.

Given their broad substrate specificity and wide usage, it is unsurprising that there have been concerted efforts by a number of different research groups to transfer this methodology to solid-support to afford easily recoverable and fully recyclable homogeneous or heterogeneous salen catalysts for asymmetric synthesis. Jacobsen et al. have immobilised salen catalysts onto polystyrene resin or silica supports, affording a recyclable homogeneous catalyst that was employed for the kinetic resolution of a range of racemic epoxides in excellent e.e. using either water or phenol as a nucleophile.[33] Zheng et al. have also employed a range of easily recyclable homogeneous oligomeric poly-salen–Co(III) complexes that catalyse the kinetic resolution of racemic epoxides in high e.e. using water as a nucleophile.[34] An alternative approach to immobilisation involving the preparation of dendrimeric salen catalysts also gave enhanced reactivity when compared to monomeric salen catalysts to afford chiral epoxides and diols in >98% e.e.,[35] whilst the use of 'light fluorous' chiral Co(salen) complexes for the HKR of terminal epoxides under essentially solvent free conditions has also been investigated.[36]

## 3. Oxidative kinetic resolution via asymmetric epoxidation strategies

The seminal protocol for the catalytic kinetic resolution of allylic alcohols first reported by Sharpless et al. in 1981 (Scheme 8)[37] continues to find favour amongst synthetic chemists for the preparation of a wide range of chiral synthons directed towards the synthesis of chiral drugs;[23] as substrates for new synthetic methodology;[38] or for natural product synthesis.[37a]




**Scheme 8.** Kinetic resolution of racemic allylic alcohols using Sharpless asymmetric epoxidation.

For example, over the last two years a range of non-racemic chiral allylic alcohol or epoxides have been prepared using this methodology as synthons for the asymmetric synthesis of a wide range of natural products such as (+)-Grandisol,[39] Korormicin,[40] (+)-Isoaltholactone,[41] (+)-Methynolide,[42] and Methyl isosartortuoate[43] (Fig. 7).

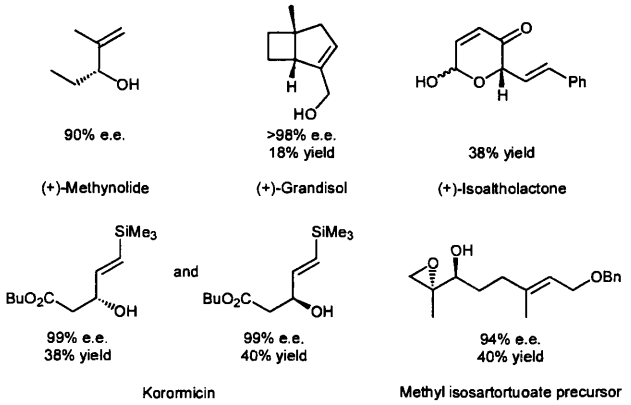
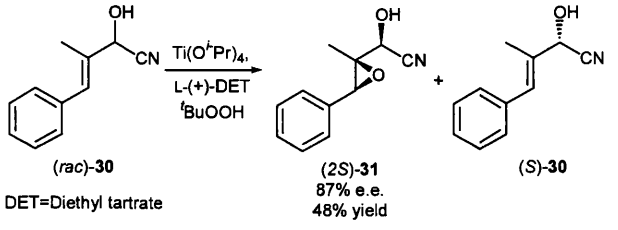



**Figure 7.** Synthons produced via Sharpless asymmetric epoxidation for natural product synthesis.

Williams et al. have reported the efficient kinetic resolution of allylic cyanohydrin (*rac*)-**30** via Sharpless asymmetric epoxidation to afford (2*S*)-**31** in 87% e.e. and 48% yield (Scheme 9).[44] Attempts to incorporate this kinetic resolution into an elegant 'one-pot' catalytic electronic activation strategy involving reversible interconversion of an achiral α,β-unsaturated aldehyde into its corresponding racemic allylic cyanohydrin, followed by kinetic resolution via stereoselective epoxidation, and subsequent transformation into a chiral α,β-epoxy aldehyde, were ultimately unsuccessful however.




**Scheme 9.** Kinetic resolution of allylic cyanohydrin (*rac*)-**30**.

In 1995 Jacobsen et al. reported the first example of a catalytic kinetic resolution using (salen)-Mn catalyst (*S,S*)-**32** (Fig. 8), *m*-CPBA and *N*-methyl-morpholine-*N*-oxide for the stereoselective epoxidation of 2,2-dialkyl chromene (*rac*)-**34** with a modest *s* value of 3.1 to afford the two diastereoisomeric epoxychroman products (*R,S,S*)-**35** and (*S,S,S*)-**36** both in >97% e.e. (Scheme 10).[45]

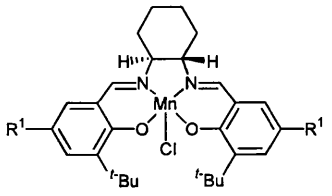
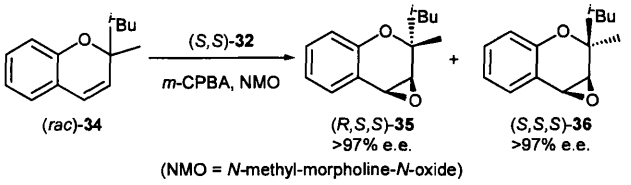
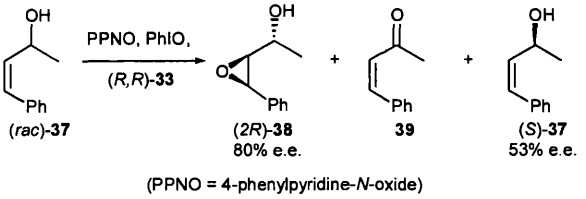



**Figure 8.**




**Scheme 10.** Kinetic resolution of 2-methyl-2-isobutyl chromene (*rac*)-**34** with catalyst (*S,S*)-**32**.

This Mn–salen complex mediated epoxidation resolution was later successfully applied to the kinetic resolution of 1,2-dihydronaphthalenes for the synthesis of lignans,[46] whilst Adam et al. have recently applied it to the kinetic resolution of aryl-substituted allylic alcohols.[47] For example, *cis*-allylic alcohol (*rac*)-**37** was resolved using catalyst (*R,R*)-**33** where its (*R*)-enantiomer was preferentially epoxidised to give the *threo* or *cis*-epoxy alcohol (2*R*)-**38** in 80% e.e., whilst the unreacted enantiomer (*S*)-**37** was recovered in 53% e.e. (Scheme 11). A small amount of the over-oxidation product enone **39** was also recovered in a ratio of (2*R*)-**38**:**39** of 95:5.




**Scheme 11.** Kinetic resolution of allylic alcohol (*rac*)-**37** via Jacobsen–Katsuki epoxidation.

An alternative method of kinetic resolution via alkene epoxidation was reported in 1999 by Shi et al.[48] using their chiral dioxirane epoxidising agent generated in situ from the action of Oxone™ on fructose derived ketone (–)-**40** (Fig. 9).[49] Thus, 1-phenyl-6-(trimethylsiloxy)cyclohexene (*rac*)-**41** was treated with 35 mol% of (–)-**40** and Oxone™ at –10°C for 2.5 h which gave recovered (*S*)-**41** in 96% e.e. at 49% conversion. *trans*-Epoxide (*S*)-**42** was shown to be formed as the predominant diastereoisomeric product in 95% e.e., with >20:1 selectivity over the corresponding *cis*-epoxide (Scheme 12).

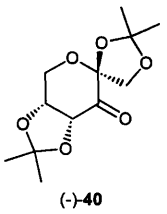



Figure 9.

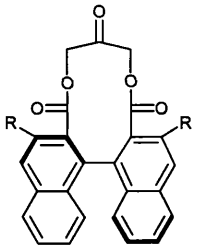
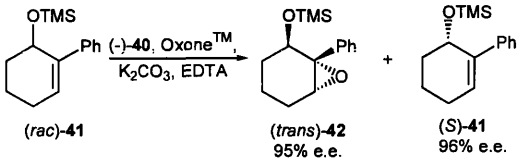



Figure 10.



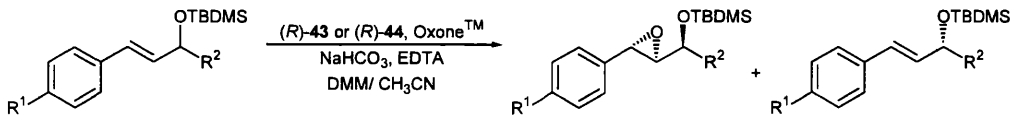

Scheme 12. Kinetic resolution of (*rac*)-**41** via dioxirane-catalysed epoxidation.

Yang et al. subsequently employed dioxiranes derived from $C_2$-symmetric binaphthyl-ketones (*R*)-**43** and (*R*)-**44** for the enantioselective epoxidation of racemic α-trichloromethyl allylic alcohols to afford synthetically useful *erythro*-epoxides in excellent e.e.[50] High selectivities were observed for substrates that contained electron donating or sterically demanding aryl groups, whilst *tert*-butyl- and trifluoromethyl substituted allylic-TBDMS ethers also afforded acceptable levels of stereoselectivity using (*R*)-**43** or (*R*)-**44** (Fig. 10) as a catalyst precursor (Table 2).

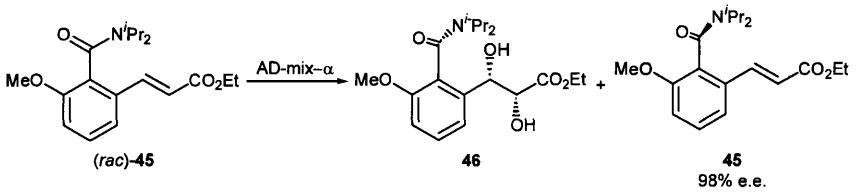
### 3.1. Kinetic resolution via asymmetric dihydroxylation

The Sharpless asymmetric dihydroxylation mechanism has proven to be a highly effective catalyst for the stereoselective dihydroxylation of alkenes, but has found only limited success as a strategy for kinetic resolution.[51] However, AD-mix-α has recently been employed for the catalytic kinetic resolution of atropisomeric amides with excellent levels of enantioselection for certain substrates. The most impressive results were obtained for α,β-unsaturated ester (*rac*)-**45**, containing an *N*,*N*-diiso-propylamide fragment, which proceeded with a $k_{rel}$ of 32 using AD-mix-α affording chiral amide **45** (and diol **46**) in 98% e.e. at 57% conversion (Scheme 13).[52]

**Table 2.** Kinetic resolution of acyclic secondary allylic silyl ethers via chiral dioxirane-mediated epoxidation



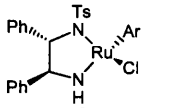

| $R^1$ | $R^2$ | Catalyst | Epoxide | | Recovered allylic ether | | *s* |
|---|---|---|---|---|---|---|---|
| | | | % Yield | e.e. | % Yield | e.e. | |
| $^t$Bu | $CCl_3$ | (*R*)-**43** | 41 | – | 41 | 96 | 13 |
| OMe | $CCl_3$ | (*R*)-**43** | 26 | – | 42 | 98 | 13 |
| H | $CCl_3$ | (*R*)-**44** | 43 | 77 | 42 | 96 | 30 |
| Et | $CCl_3$ | (*R*)-**44** | 38 | 77 | 43 | 99 | 37 |
| $^t$Bu | $CCl_3$ | (*R*)-**44** | 41 | 93 | 44 | 94 | 100 |
| H | $^t$Bu | (*R*)-**44** | 44 | 76 | 43 | 63 | 14 |
| H | $CF_3$ | (*R*)-**44** | 41 | – | 43 | 75 | 9 |




Scheme 13. Kinetic resolution of atropisometric amide (*rac*)-**45** using AD-mix-α.

### 3.2. Kinetic resolution via asymmetric oxidation of racemic secondary alcohols

A large number of kinetic resolution strategies that rely on the use of chiral catalysts for the enantioselective oxidation of one enantiomer of a racemic secondary alcohol to its corresponding ketone have been reported to date.[53] Since Noyori's seminal report in 1997 on reversible catalytic asymmetric transfer hydrogenation complexes for asymmetric catalysis, the use of chiral diamine Ru(II) complexes to transfer hydride from a racemic alcohol substrate to acetone has been widely used as a method for the kinetic resolution of secondary alcohols.[54] For example, Ogasawara et al. have employed complexes (*S*,*S*)-**47** or (*S*,*S*)-**48** (Fig. 11) for the kinetic resolution of a range of cyclic allylic alcohols in good e.e., which were subsequently used as synthons for the asymmetric synthesis of a wide range of natural products including (−)-Chokol G,[55] (+)-Frontalin and (−)-Malyngolide,[56] (+)-Tanikolide[57] (−)-Morphine,[58] 25-hydroxy-Grundmann's ketone,[59] and (+)-Vernolepin (Fig. 12).[60]




(*S*,*S*)-**47**: Ar=$\eta^6$-mesitylene
(*S*,*S*)-**48**: Ar=$\eta^6$-cymene

**Figure 11.**

The use of Wills' amino-2-indanol derived catalyst (1*R*,2*S*)-**49**[61] (Fig. 13) for the kinetic resolution of secondary alcohols has also been investigated and shown to afford excellent levels of enantioselectivity for the oxidation of a range of racemic α- and β-aryl alcohols.[62] Interestingly, Faller et al. have employed this catalyst to develop a tandem protocol employing 'mirror image catalysts' to enhance the enantiomeric excess of target

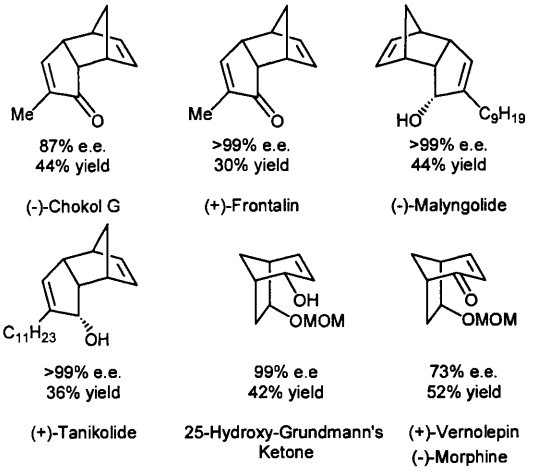
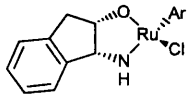



**Figure 12.** Synthons resolved for natural product synthesis via enantioselective oxidation using **47** or **48**.

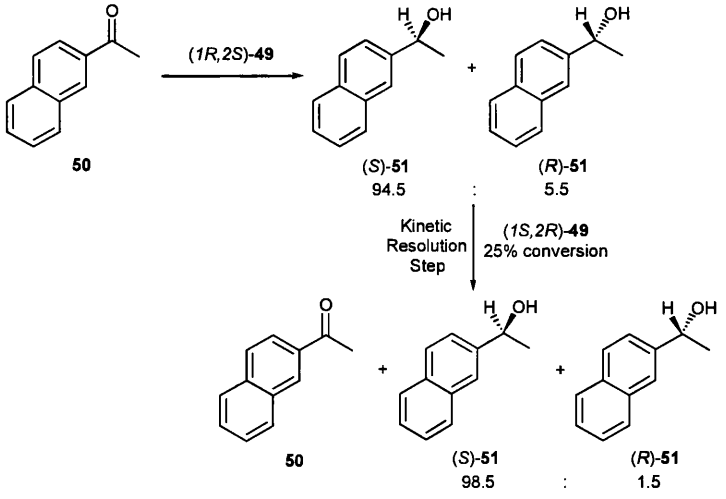
alcohols. For example, reduction of ketone **50** with catalyst (1*R*,2*S*)-**49** in the presence of excess 2-propan-2-ol afforded alcohol (*S*)-**51** in 89% e.e., which was then oxidised with the antipode of catalyst (1*S*,2*R*)-**49** in the presence of excess acetone enabling recovery of (*S*)-**51** in an enhanced 97% e.e. at 25% conversion (Scheme 14).




Ar =$\eta^6$-*p*-cymene
(1*R*,2*S*)-**49**

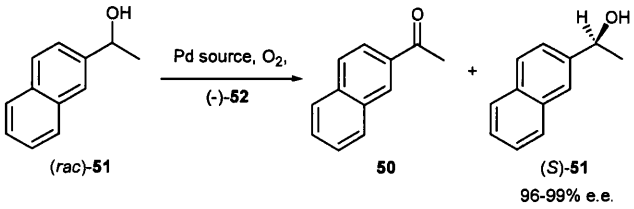
**Figure 13.**

In 2001, Sigman et al. and Stoltz et al. independently reported a Pd(II)-catalysed oxidative kinetic resolution of a combined total of nine different secondary racemic aryl alcohols using (−)-sparteine **52** (Fig. 14) as a chiral ligand




**Scheme 14.** Kinetic resolution of scalemic secondary alcohol **51** catalysed by (1*S*,2*R*)-**49**.

and molecular oxygen as the terminal oxidant (Scheme 15).[63,64] In a representative example, Sigman et al. used $Pd(OAc)_2$ as a palladium source, which gave unreacted alcohol (*S*)-**51** in 96% e.e.,[63] whilst Stoltz et al. found that the alternative use of $Pd(nbd)Cl_2$ resulted in the e.e. of the recovered alcohol (*S*)-**51** being increased to 99%.[64] This methodology has recently been exploited for the synthesis of (*S*)-3-phenyl-3-hydroxypropyl tosylate in 95% e.e., which was used in the synthesis of the chiral drugs (*R*)-tomoxetine and (*S*)-fluoxetine.[65] Interestingly, O'Brien et al. have recently reported the use of an alternative chiral diamine (+)-**53** [derived from (−)-cystine] (Fig. 15) as a (+)-sparteine surrogate for the oxidative kinetic resolution of indan-1-ol which afforded indanone **55** and recovered (*R*)-**54** in 80% e.e. (Scheme 16), albeit with inferior stereocontrol to that observed for sparteine (−)-**52** which afforded (*S*)-**54** in 98% e.e.[66]




**Scheme 15.** Kinetic resolution of secondary alcohols via Pd(II)-catalysed oxidation.

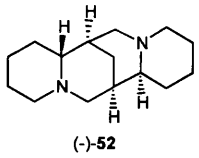
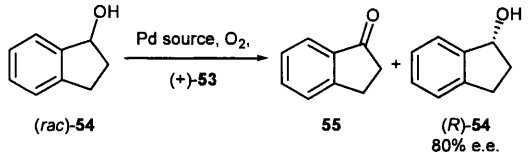



**Figure 14.**




**Scheme 16.** Pd(II)-catalysed kinetic resolution of indan-1-ol with diamine (+)-**53**.

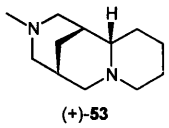



**Figure 15.**

Studies into the mechanism of this class of oxidative resolution were disclosed in 2002 by Sigman et al.[67] who found that the Pd[(−)-sparteine]$Cl_2$ complex was ineffective as a catalyst without excess (−)-sparteine acting as an exogenous base to control both the reactivity and selectivity of the catalytic process. This discovery implied that the reaction proceeds via a base-promoted pathway, in which a palladium (*S*)-alkoxide is formed stereoselectively, followed by hydride elimination to afford the corresponding ketone (Fig. 16). The excess (−)-sparteine then acts as a base to deprotonate the bound alcohol thus facilitating the catalytic cycle, with stoichiometric $O_2$ acting as the terminal oxidant.

An interesting approach to the kinetic resolution of *tert*-cyclobutanols has been described involving Pd(0) mediated C–C bond cleavage of cyclobutanols (*rac*)-**57a–d** in the presence of chiral ferrocenyl ligand (*R*,*S*)-**56** (Fig. 17) with moderate to good enantioselectivities.[68] The

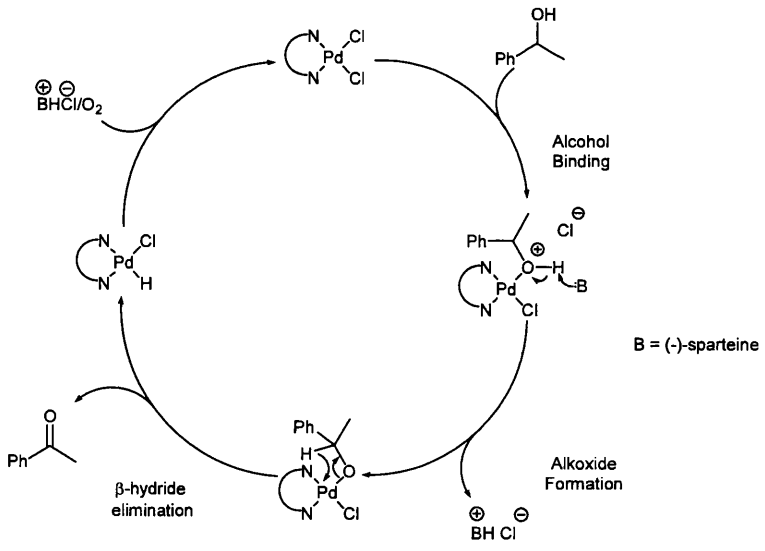
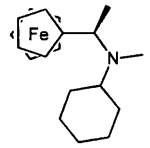



**Figure 16.** Proposed catalytic cycle for the oxidation of secondary alcohols catalysed by a Pd(II) complex.




(*R*,*S*)-**56**

Figure 17.

range of *tert*-cyclobutanols (*rac*)-**57a–d** that were resolved to afford ring opened ketones **58a–d** are described in Scheme 17, whilst the mechanism by which this resolution is proposed to proceed is described in Fig. 18.

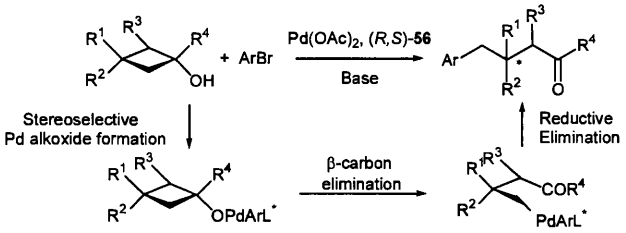
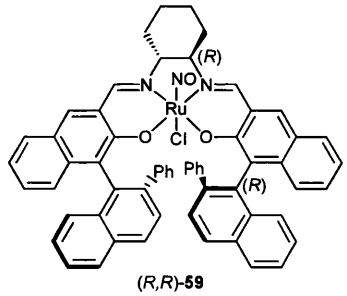


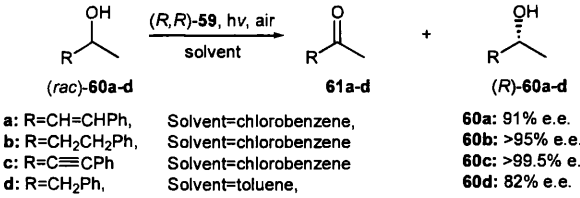

**Figure 18.** Proposed mechanism for the Pd-mediated resolution of (*rac*)-**57a–d**.

An alternative approach to $O_2$-mediated oxidative resolution has been disclosed by Katsuki et al. who employed chiral (nitroso)–salen–Ru complexes for the stereoselective oxidation of a range of secondary alcohols under photolytic conditions. Thus, photolysis of solutions of alcohols (*rac*)-**60a–d** in aromatic solvents, in the presence of catalyst (*R*,*R*)-**59** (Fig. 19) under aerobic conditions, resulted in efficient kinetic resolution to afford ketones **61a–d** and recovered alcohols (*R*)-**60a–d** in 82 to >99% e.e. (Scheme 18).[69]



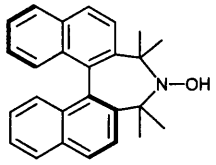

(*R*,*R*)-**59**

Figure 19.



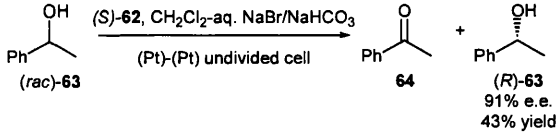

**Scheme 18.** Kinetic resolution of secondary alcohols (*rac*)-**60a–d** catalysed by (*R*,*R*)-**59**.

Building on previous work employing chiral nitroxyl radicals for enantioselective oxidation,[70] Tanaka et al. reported the kinetic resolution of six secondary racemic arylalcohols via electrochemical oxidation with *s* values ranging from 5.3 to 20.[71] This approach involved electro-oxidation in the presence of a catalytic amount of an enantiomerically pure binaphthyl tertiary *N*-hydroxylamine (*S*)-**62** (Fig. 20) which was performed using a simple undivided cell under constant current.[72] For example, electro-oxidation of 1-phenyl-1-ethanol (*rac*)-**63** proceeded to give acetophenone **64** in 57% yield and unreacted alcohol (*R*)-**63** in 91% e.e. and 43% yield (Scheme 19).



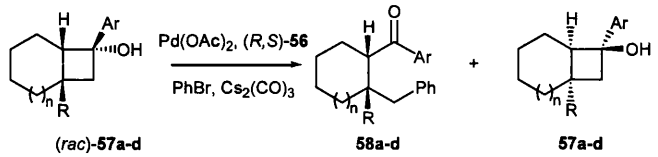

(*S*)-**62**

**Figure 20.**




**Scheme 19.** Kinetic resolution of (*rac*)-**63** via electro-oxidation in the presence of catalyst (*S*)-**62**.

The oxidative catalytic cycle proposed for this kinetic resolution is described in Figure 21, in which catalyst (*S*)-**62** is oxidised electrochemically to afford **65**, which then preferentially reacts with one enantiomer of 1-phenyl-1-ethanol (*S*)-**63** to afford adduct **66**, that then decomposes via a cyclic transition state regenerating **62**, thus affording acetophenone **64** and recovered phenylethan-1-ol (*R*)-**63**.




The absolute stereochemistry of the product ketones **58a-d** and recovered alcohols **57a-d** in these reactions were not determined

**Scheme 17.** Palladium-catalysed kinetic resolution of (*rac*)-*tert*-cyclobutanols **57a–d**.

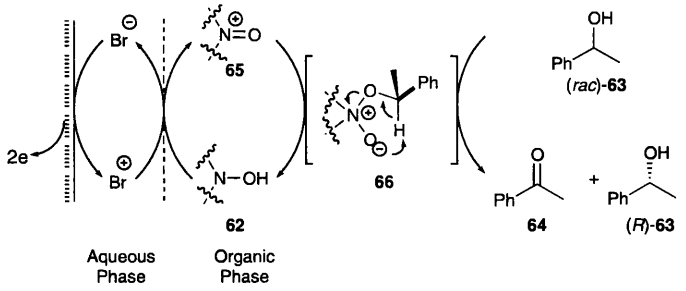
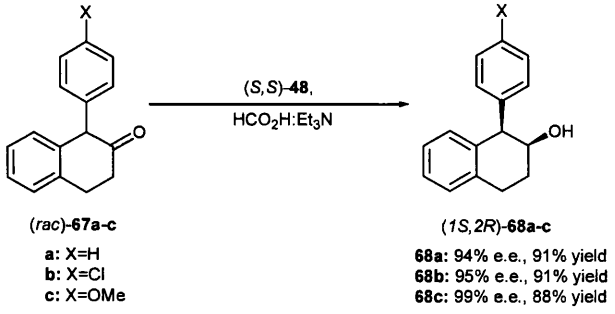



**Figure 21.** The electro-oxidative cycle for the kinetic resolution of (*rac*)-**63**.

The use of an alternative dipeptide derived oxidation catalyst containing a nitroxyl-containing α-amino acid 2,2,6-tetramethylpiperidine-1-oxyl-4-amino-4-carboxylic acid, and a β-turn inducing L-α-methyl-valine substituent, have also afforded limited success for this type of oxidative resolution, with the best results affording recovered phenylethan-1-ol (*S*)-**63** in 75% e.e.[73]

## 4. Kinetic resolution via enantioselective reduction of racemic ketones

Racemic ketones that contain configurationally labile α-stereogenic centres often undergo efficient dynamic kinetic resolution (DKR) when they are reduced using Noyori's asymmetric transfer hydrogenation catalysts.[74] For example, a series of 1-aryl-2-tetralones (*rac*)-**67a–c** have recently been subjected to DKR using a RuTsDPEN hydrogenation catalyst (*S,S*)-**48** to afford a small library of the corresponding alcohols (1*S*,2*R*)-**68a–c** containing two stereogenic centres in >93% e.e. and >87% yield (Scheme 20).[75]




**Scheme 20.** DKR of cyclic ketones (*rac*)-**67a–c** via transfer hydrogenation using (*S,S*)-**48**.

In 2002, Noyori et al. introduced a new type of highly efficient chiral Ru–binaphthyl complex (*S,R,R*)-**69** (Fig. 22) for the kinetic resolution of ketones under non-alkaline conditions, that enables easily racemisable ketones such as 2-isopropylcyclohexanone (*rac*)-**70** to be efficiently resolved to afford unreacted ketone (*S*)-**70** in 91% e.e., and *syn*-alcohol (1*R*,2*R*)-**71** in 85% e.e. at 53% conversion (Scheme 21).[76]

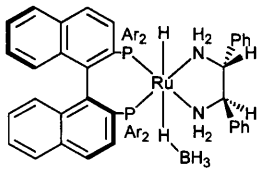
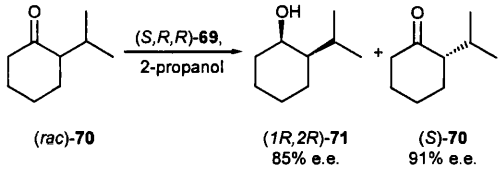
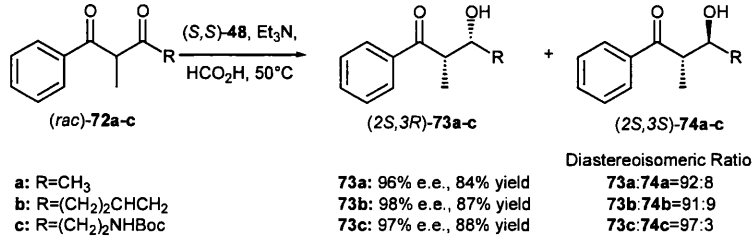



**Figure 22.**

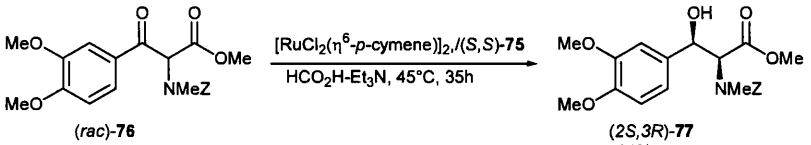



**Scheme 21.** DKR of 2-isopropylcyclohexanone (*rac*)-**70** using Ru-complex (*S,R,R*)-**69**.

Noyori's original asymmetric Rh-catalysed hydrogenation catalysts continue to be popular for the dynamic kinetic resolution of β-dicarbonyl compounds in high e.e.,[77] where Cossy et al. have recently extended the use of this methodology to the kinetic resolution of racemic 2-alkyl-1,3-diketones.[78] They found that treatment of diketones (*rac*)-**72a–c** with (*S,S*)-**48** in the presence of formic acid and triethylamine resulted in a mixture of alcohols *syn*-(2*S*,3*R*)-**73a–c** and *anti*-(2*S*,3*S*)-**74a–c**, with the major *syn*-alcohols (2*S*,3*R*)-**73a–c** being formed as the major diastereoisomer in good enantiomeric excess in all cases (Scheme 22).




**Scheme 22.** DKR of β-diketones (*rac*)-**72a–c** via transfer hydrogenation.




**Scheme 23.** DKR of α-amido-β-keto acid (*rac*)-**76** via transfer hydrogenation.

Wagner et al. have attempted to improve the performance of Noyori's catalytic system by the introduction of a more electron-withdrawing trifluorosulfonyl group into the chiral ligand design.[79] It was found that when ligand (*S,S*)-**75** (Fig. 23) was employed in place of (*S,S*)-**48** for the DKR of *threo*-β-hydroxy α-amido acid (*rac*)-**76**, that the e.e. of (2*S*,3*R*)-**77** was improved from 94 to 98%, whilst the yield was improved from 80 to 100%, and the reaction time decreased from 72 to 35 h (Scheme 23).

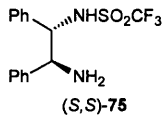
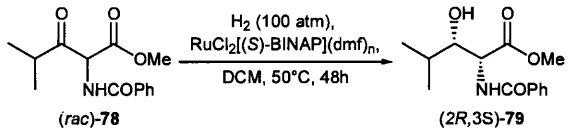



**Figure 23.**

In 2001, Hamada et al. also described an efficient synthesis of (2*R*,3*S*)- and (2*S*,3*S*)-**3**-hydroxyleucines via DKR using $RuCl_2$[(*S*)-BINAP](dmf)$_n$-catalysed hydrogenation.[80,81] The DKR of β-keto-α-amido acid ester (*rac*)-**78** was performed at 50°C in DCM under 100 atmospheres of $H_2$, resulting in the 3-hydroxy-leucine derivative (2*R*,3*S*)-**79** being formed in 99% e.e. and 100% yield, which is a key structural motif within a number of naturally occurring cyclic depsipeptides (Scheme 24).




**Scheme 24.** DKR of α-amido-β-keto-ester (*rac*)-**78** via hydrogenation.

In 2000, Genêt et al. reported the highly stereoselective synthesis of the functionalised hexahydroazepine core of (−)-Balanol (a protein kinase C inhibitor) through DKR of a racemic α-amido-β-keto ester using a Ru(II)-catalysed hydrogenation reaction.[82] Thus, the reduction of α-amido-β-keto ester (*rac*)-**81** with 1 mol% Ru complex of MeO-BIPHEP (*R*)-**80** (Fig. 24) at 50°C in DCM for 96 h afforded (2*S*,3*R*)-**82** in 94% e.e. and 93% d.e., in an overall yield of 80% (Scheme 25).

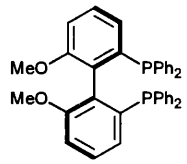
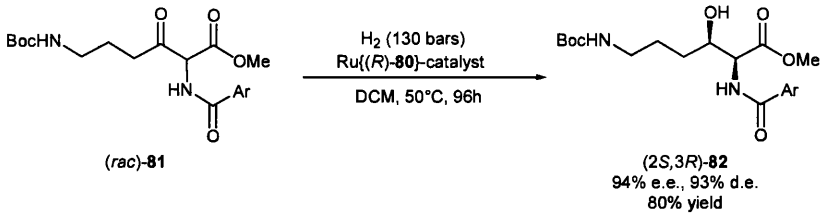
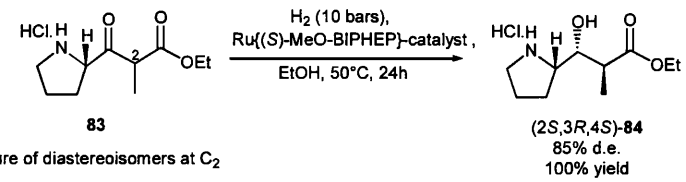



**Figure 24.**

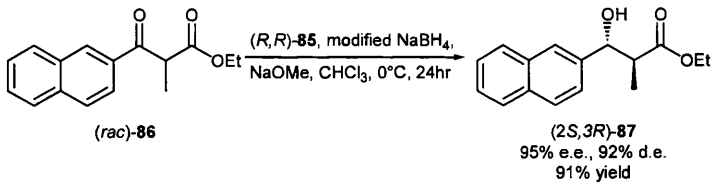
The use of the same Ru-catalyst for the synthesis of *iso*-Dolaproine via DKR was also described in which hydrogenation of a diastereoisomeric mixture of proline derived γ-amino-β-keto esters **83** with 1 mol% of Ru[MeO-BIPHEP (*S*)-**80**] at 10 bar $H_2$ at 50°C for 24 h afforded β-hydroxy ester (2*S*,3*R*,4*S*)-**84** in quantitative yield in 85% d.e. (Scheme 26).[83]




**Scheme 25.** DKR of α-amido-β-keto ester (*rac*)-**81** via hydrogenation.




**Scheme 26.** DKR of diastereoisomeric mixture of proline derived γ-amino β-keto ester **83**.




**Scheme 27.** DKR of (*rac*)-**86** via enantioselective borohydride reduction using (*R,R*)-**85**.

In 2002, Yamada et al. reported a DKR protocol based on enantioselective borohydride mediated reduction of β-keto esters catalysed by chiral β-ketoiminato Co(II) complexes (*R,R*)-**85**. For example,[84] borohydride reduction of 2-methyl-3-(2-naphthyl)-3-oxopropionic acid ethyl ester (*rac*)-**86** in the presence of 4 mol% of (*R,R*)-**85** (Fig. 25) at 0°C afforded β-hydroxy-ester (2*S*,3*R*)-**87** in 95% e.e., 92% d.e., and in 91% yield (Scheme 27).

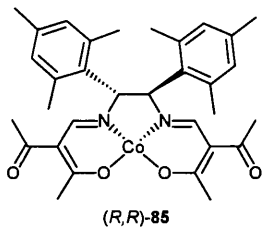
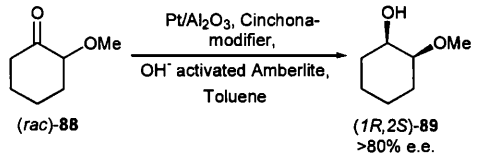



**Figure 25.**

Studer et al. have also reported that heterogeneous *Cinchona*-modified $Pt/Al_2O_3$ catalysts can be employed for the reductive kinetic resolution of a range of racemic α-keto ethers in good to excellent e.e. at conversions of less than 50%. This approach was extended to the dynamic kinetic resolution of 2-methoxycyclohexanone (*rac*)-**88**, in the presence of basic ion exchange resins as a solid supported base to facilitate efficient racemisation, to afford *syn*-α-methoxy alcohol (1*R*,2*S*)-**89** in >80% e.e. at 95% conversion (Scheme 28).[85]




**Scheme 28.** DKR of 2-methoxycyclohexanone (*rac*)-**88** with Cinchona-modified $Pt/Al_2O_3$.

The use of oxazaborolidine-catalysed asymmetric reductions[86] for kinetic resolutions is an increasingly popular approach; however, the majority of reports to date have employed stoichiometric amounts of catalyst for efficient resolution.[87] In 2001, Kagan et al. described lengthy optimisation studies into the use of this class of catalyst for the kinetic resolution of 4-acetyl[2.2]paracyclophane (*rac*)-**91**, with the best enantioselectivities being observed when 15 mol% of chiral oxazaborolidine (*S*)-**90** (Fig. 26) and 0.6 equiv. of borane were employed for resolution to afford recovered (*S*)-**91** in 98% e.e. and alcohols (*R,R*)-**92** and (*R,S*)-**93** in 89% e.e. and >99% e.e., respectively (Scheme 29).[88]

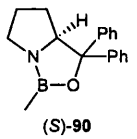
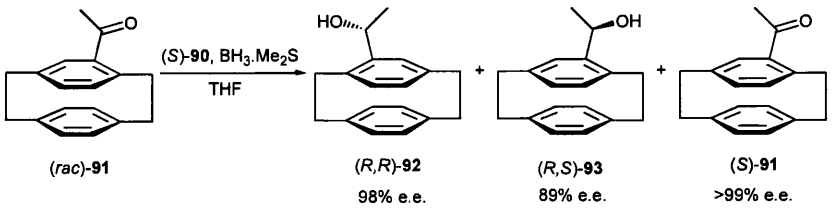



**Figure 26.**

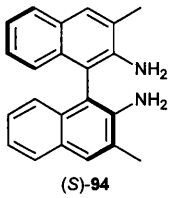
### 4.1. Kinetic resolution via asymmetric hydrogenation of alkenes

Mikami et al. have employed the use of their ingenious 'chiral poisoning' approach[89] to devise an efficient protocol for the kinetic resolution of racemic allylic alcohols using *racemic* $RuCl_2$[XylBINAP](dmf)$_n$ as catalyst. They found that addition of 0.5 equiv. of 3,3′-dimethyl-1,1′-binaphthyl-2,2′-diamine (DM-DABN) (*S*)-**94** (Fig. 27) to racemic $RuCl_2$[XylBINAP](dmf)$_n$ resulted in enantioselective complexation of the (*S*)-$RuCl_2$-[XylBINAP] enantiomer, thus enabling free uncomplexed (*R*)-$RuCl_2$[XylBINAP] to catalyse the kinetic resolution of 2-cyclohexen-1-ol (*rac*)-**95** with an *s* value



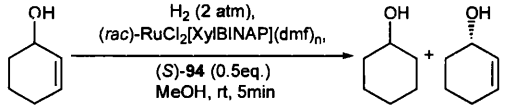

**Scheme 29.** Kinetic resolution of 4-acetylparacyclophane (*rac*)-**91** using oxazaborolidine (*S*)-**90**.

of 102, affording cyclohexanol **96** and recovered allylic alcohol (*S*)-**95** in 100% e.e. at 53% conversion (Scheme 30).[90]



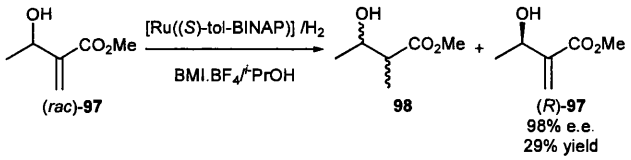

(*S*)-**94**

**Figure 27.**




**Scheme 30.** Kinetic resolution of (*rac*)-**95** via stereoselective complexation of one enantiomer of (*rac*)-$RuCl_2$[(*S*)-BINAP](dmf)$_n$ using (*S*)-**94**.

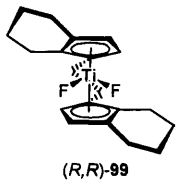
In 2001, Dupont et al. reported the influence of hydrogen pressure on the directed asymmetric hydrogenation of methyl-3-hydroxy-2-methylenebutanoate (*rac*)-**97** catalysed by [$RuCl_2$-(*S*)-tolyl-BINAP]$_2$·$NEt_3$ using the ionic liquid $^n$butyl-methylimidazolium tetrafluoroborate (BMI·$BF_4$) as solvent under various conditions.[91] It was found that the best kinetic resolution was obtained at a pressure of 40 atmospheres of hydrogen affording β-hydroxy ester **98**, with unreacted substrate (*R*)-**97** being recovered in 98% e.e. and 29% yield (Scheme 31). It was found that $k_{rel}$ for this resolution was influenced considerably by hydrogen pressure, with a significant drop to 85% e.e. being observed for (*R*)-**97** at higher pressure (50 atmospheres).




**Scheme 31.** Kinetic resolution of methyl 3-hydroxy-2-methylenebutanoate (*rac*)-**97** via asymmetric hydrogenation.

## 4.2. Catalytic hydrosilylation or hydroboration strategies for kinetic resolution

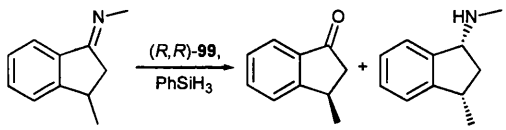
In 2000, Buchwald and Yun described the efficient kinetic resolution of *N*-methyl imines of 3-substituted indanones and 4-substituted tetralones via hydrosilylation with chiral titanocene catalyst, (EBTHI)$TiF_2$ (*R*,*R*)-**99** (Fig. 28).[92] Hydrosilylation of the *N*-methyl imine of 3-substituted indanones (*rac*)-**100** was carried out employing 1 mol% of catalyst (*R*,*R*)-**99**, which was complete after 2 h at 0°C giving at ~50% conversion




(*R*,*R*)-**99**

**Figure 28.**

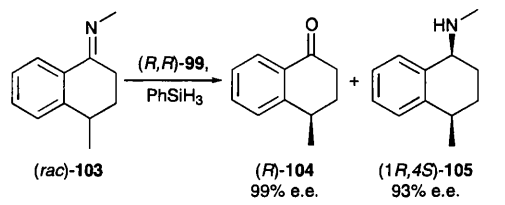
recovered ketone (*R*)-**101** with 93% e.e. (after hydrolysis of unreacted starting material) with the major amine product (1*R*,3*S*)-**102** being obtained in 83% e.e. in high d.e. (Scheme 32). It was found that lowering the reaction temperature increased the *s* value of the resolution at the expense of the reaction rate; thus decreasing the e.e. of recovered ketone (*R*)-**101**, whilst increasing the e.e. of the product amine (1*R*,3*S*)-**102**.



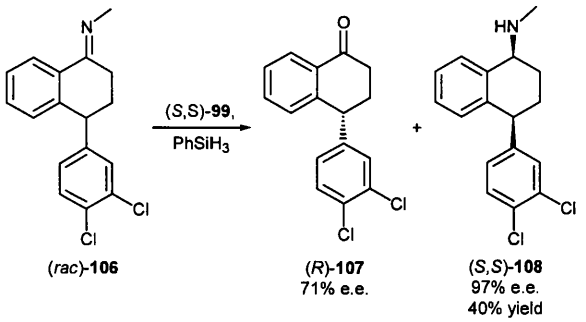

**Scheme 32.** Kinetic resolution of *N*-methyl imine (*rac*)-**100** with (*R*,*R*)-**99**.

The resolution of racemic *N*-methyl 4-substituted tetralones was also investigated and found to afford better results with *s* values ranging from 18 to 78 at room temperature. For example, the resolution of tetralone (*rac*)-**103** occurred with an *s* value of 60.8, giving recovered ketone (*R*)-**104** in 99% e.e., and the major diastereoisomeric amine (1*R*,4*S*)-**105** in 93% e.e. (Scheme 33).

This approach has been utilised for the asymmetric synthesis of a range of chiral amine products including sertraline [(+)-*cis*-1-methylamino-4-(3,4-dichlorophenyl) tetralin] (*S*,*S*)-**108**, an antidepressant sold by Pfizer under the name of Zoloft as a competitive inhibitor of synaptosomal serotonin uptake. Using this method, sertraline precursor (*rac*)-**106** was exposed to a catalytic quantity (2.5 mol%) of (*S*,*S*)-**99** using $PhSiH_3$ as a stoichiometric reductant to afford sertraline (*S*,*S*)-**108** in 97% e.e. and 40% yield, whilst ketone (*R*)-**107** was recovered in 71% e.e. (Scheme 34).[93]




**Scheme 33.** Kinetic resolution of *N*-methyl imine (*rac*)-**103** with (*R*,*R*)-**99**.




**Scheme 34.** Synthesis of sertraline (*S*,*S*)-**108** via kinetic resolution of (*rac*)-**106**.

Brown et al. have reported an alternative formal asymmetric synthesis of sertraline based on the use of QUINAP–Rh complex (*S*)-**109** (Fig. 29) for the stereoselective hydroboration of 1-aryl-dihydronaphthalene (*rac*)-**110** to afford alcohol (1*S*,4*R*)-**111** and the recovered unreacted 1-aryl-dihydronaphthalene (*S*)-**110** in 98% e.e. and 78% yield. Subsequent hydroamination of (*S*)-**110** using (*S*)-**109** resulted in Sertraline (*S*,*S*)-**108** being formed as the minor diastereoisomer in a 29:71 *cis*:*trans* isomeric mixture containing amine (1*R*,4*S*)-**112** as the major diastereoisomer (Scheme 35).[94]

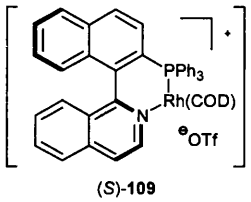



**Figure 29.**

## 5. Kinetic resolution using chiral acylation catalysts

The development of methodology for the resolution of secondary alcohols using chiral acylation catalysts continues to be a popular theme amongst the synthetic community.[95] Building on their original work using chiral phosphines such as (*S*,*S*)-**113**, Vedejs et al. have reported on the development of a second generation chiral phosphine acyl transfer catalyst (1*R*,2*R*,4*S*,5*S*)-**114** (Fig. 30) which was shown to resolve 1-(*o*-methylphenyl)ethanol (*rac*)-**115** to afford unreacted alcohol (*S*)-**115** in 98% e.e., and ester (*R*)-**116** in 95% e.e. at 51% conversion (Scheme 36).[96] The scope of this type of phosphine catalyst was subsequently demonstrated for the kinetic resolution of a small library of twelve allylic alcohols (*rac*)-**117a–d**, typically affording isobutyryl esters (*R*)-**118a–d** and unreacted alcohols (*S*)-**117a–d** in satisfactory to excellent e.e. (Scheme 37).[97]

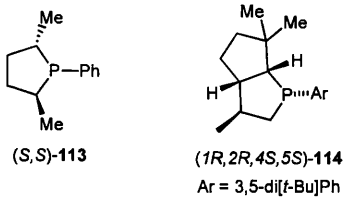
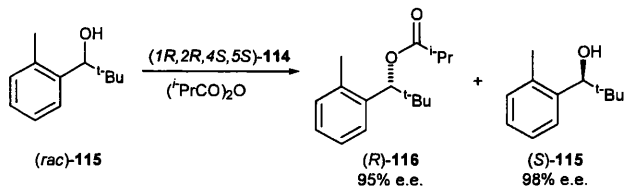
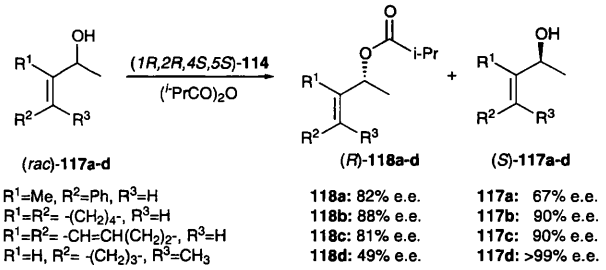


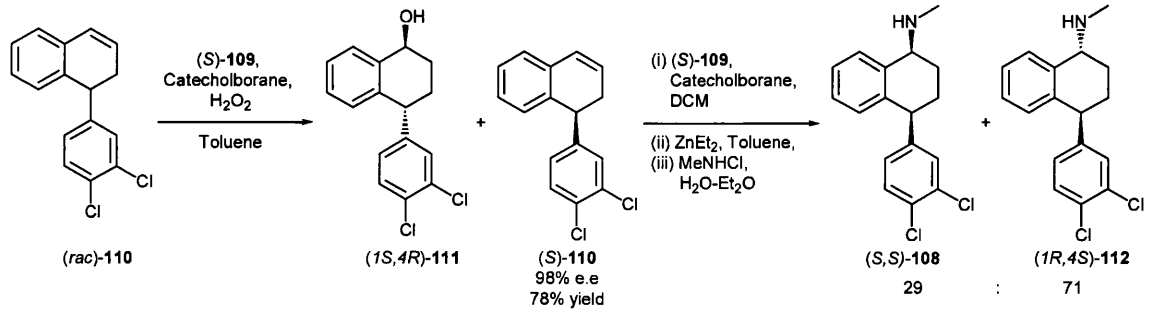

**Figure 30.**




**Scheme 36.** Kinetic resolution of (*rac*)-**115** with $^t$butyric anhydride and **114**.

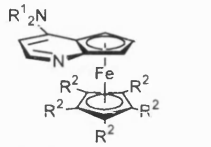



**Scheme 37.** Kinetic resolution of allylic alcohols (*rac*)-**117a–d** with isobutyric anhydride and **114**.



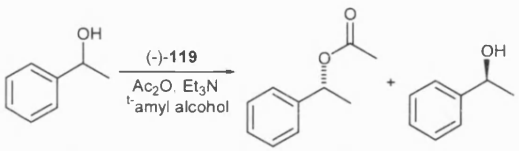

**Scheme 35.** Synthesis of Sertraline (*S*,*S*)-**108** via asymmetric hydroboration using (*S*)-**109**.

The versatile ferrocene derived acyl transfer catalysts (−)-**119** and (−)-**120** (Fig. 31) described by Fu et al. remain one of the most effective systems for the kinetic resolution of a wide range of racemic arylalkylcarbinols, including phenylethanol (*rac*)-**63** which gave ester (*R*)-**121** in 90% e.e., and unreacted alcohol (*S*)-**63** in 99% e.e. (Scheme 38).[98] These catalyst systems have recently been employed for the resolution of a series of racemic allylic alcohols to afford a wide range of structurally diverse chiral allylic alcohols such as (*R*)-**117a** in >90% e.e.[99]




(-)-**119** $NR^1{}_2$=$NMe_2$, $R^2$=Ph
(-)-**120** $NR^1{}_2$=pyrrolidino, $R^2$=Me

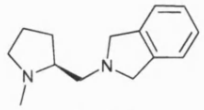
**Figure 31.**




**Scheme 38.** Kinetic resolution of (*rac*)-**63** with acetic anhydride and catalyst (−)-**119**.

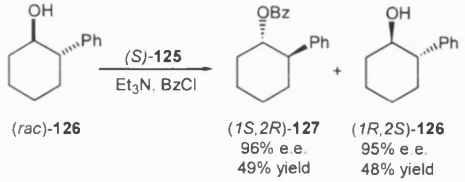
In an important breakthrough, Fu et al. have recently reported that this catalytic system can be extended to the kinetic resolution of a series of secondary arylamines (*rac*)-**122a–e** using *O*-acylated β-naphthyl-azlactone **123** as a stoichiometric carbonyl donor in the presence of catalyst (−)-**120** to afford chiral carbamates (*S*)-**124a–e** and recovered amines (*R*)-**122a–e** with *s* values >12 (Scheme 39).[100]

In 1999, Oriyama et al. reported an alternative method for the kinetic resolution of a wide range of cyclic racemic alcohols,[101] involving treatment with benzoyl chloride in the presence of 0.3 mol% of chiral diamine (*S*)-**125** (Fig. 32). For example, under these conditions benzoate ester (1*S*,2*R*)-**127** was formed in 96% e.e. and 49% yield, whilst the unreacted alcohol (1*R*,2*S*)-**126** was recovered in 95% e.e. and 48% yield (Scheme 40). This system has subsequently been employed for the kinetic resolution of a range of cyclic racemic β-halohydrins to afford the corresponding benzoate esters and recovered alcohols in fair to excellent e.e.[102]



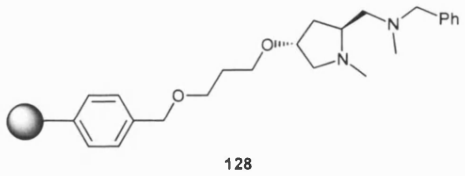

(*S*)-**125**

**Figure 32.**



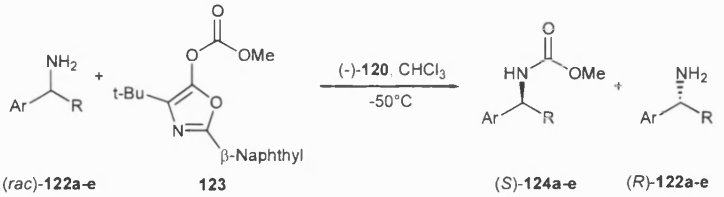

**Scheme 40.** Catalytic asymmetric benzoylation of (*rac*)-**126** using (*S*)-**125**.

This type of proline based diamine has also been immobilised onto poly(ethylene glycol) (PEG) supports and used as recyclable acylation catalysts for the kinetic resolution of a range of racemic secondary alcohols with *s* values similar to those obtained using the soluble catalyst (*S*)-**125**.[103] This class of acyl transfer catalyst has also been attached to soluble polymer supports with *J*and*J*el supported catalyst **128** (Fig. 33) affording benzoate ester (1*S*,2*R*)-**127** in 96% e.e. and recovered unreacted alcohol (1*R*,2*S*)-**126** in 85% e.e.




**128**

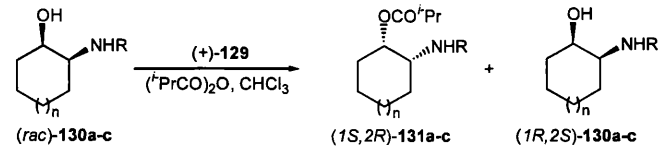
**Figure 33.**



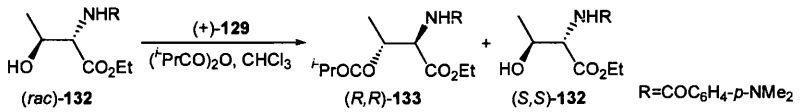

(*rac*)-**122a-e** **123** (*S*)-**124a-e** (*R*)-**122a-e**

**122a:** Ar=Ph, R=Me, *s*=12
**122b:** Ar=α-naphthyl, R=Me, *s*=27
**122c:** Ar=*o*-tol, R=Me, *s*=16
**122d:** Ar=*m*-MeO-$C_6H_4$, R=Me, *s*=22
**122e:** Ar=Ph, R=Et, *s*=16

**Scheme 39.** Kinetic resolutions of (*rac*)-amines **122a–e** catalysed by (−)-**120**.




**Scheme 41.** Kinetic resolution of (*rac*)-**130a–c** catalysed by (+)-**129**.




**Scheme 42.** Kinetic resolution of acyclic α-amido-β-hydroxy ester (*rac*)-**132** with (+)-**129**.

Another class of chiral dimethylaminopyridine like catalyst (+)-**129** (Fig. 34) has been reported for the kinetic resolution of cyclic *N*-acyl-β-amino alcohols (*rac*)-**130a–c** that selectively afforded esters (1*S*,2*R*)-**131a–c** as major products and (1*R*,2*S*)-**130a–c** in very high e.e. (Scheme 41).[104] Thus, at relatively high conversions, excellent enantioselectivities were obtained for recovered five-, six- and seven-membered *cis*-*N*-acyl-β-amino alcohols (1*R*,2*S*)-**130a–c**, respectively. Although the selectivity observed for acyclic β-amino alcohols was generally poor, *anti*-β-amino alcohol (*rac*)-**132** was shown to be enantioselectively acylated to afford ester (*R*,*R*)-**133**, enabling *N*-acyl-β-amino alcohol (*S*,*S*)-**132** to be recovered in 93% e.e. at 70% conversion (Scheme 42).[105]

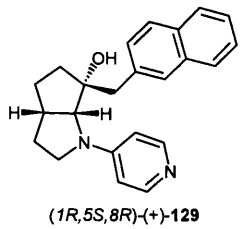
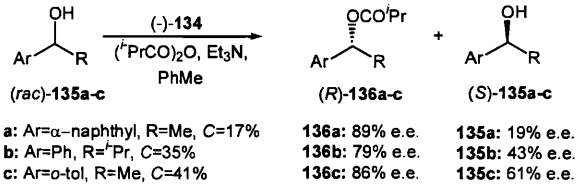



**Figure 34.**

Spivey et al. have continued to explore the use of their axially chiral analogues of 4-(dimethylaminopyridine),[106] with atropisomeric biaryl diamine (–)-**134** (Fig. 35) having proved the most successful catalyst for the resolution of aryl-alcohols (*rac*)-**135a–c** to date, affording esters (*R*)-**136a–c** in moderate to good e.e. at low conversion (Scheme 43).[107] The use of $C_2$-symmetric analogues of 4-(pyrrolidino)-pyridine (*R*,*R*)-**137** for related kinetic resolutions proved less successful however (Fig. 36).[108]




**Scheme 43.** Kinetic resolution of aryl-alcohols (*rac*)-**135a–c** catalysed by (–)-**134**.

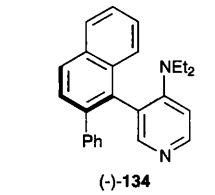



**Figure 35.**

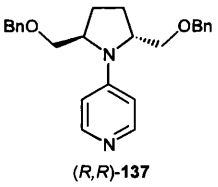



**Figure 36.**

Jeong et al. have reported a new tertiary amine based nucleophilic DMAP analogue (–)-**138** (Fig. 37) that gives good to excellent results for the resolution of racemic alkylarylcarbinols.[109] It was found that the *s* values for this catalyst increased as the steric bulk of the alkyl group of the alcohol substrate increased, with the best result being obtained for acylation of racemic *trans*-2-phenylcyclohexanol (Table 3, entry 6) which proceeded with $s = 21$ giving recovered (1*S*,2*R*)-alcohol in 99% e.e. and the (1*R*,2*S*)-ester product in 62% e.e.

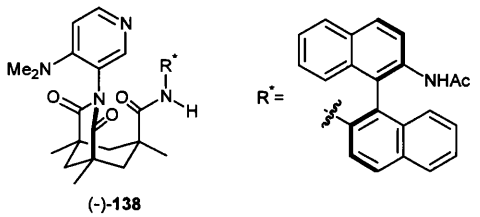



**Figure 37.**

**Table 3.** Kinetic resolution of racemic secondary alcohols with catalyst (−)-**138**

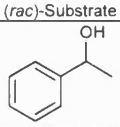
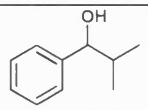
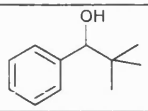
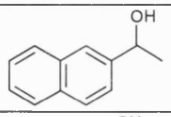
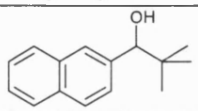
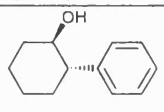
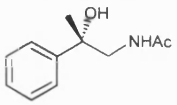
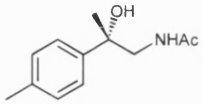
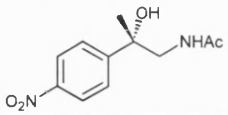
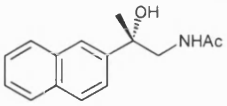
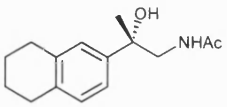
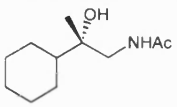
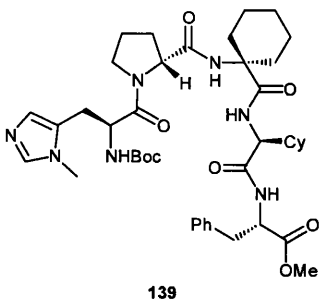
| Entry | (*rac*)-Substrate | *C*/% | e.e./% | | *s* |
|---|---|---|---|---|---|
| | | | (*S*)-Alcohol | (*R*)-Ester | |
| 1 |  | 70 | 79 | 34 | 4.4 |
| 2 |  | 77 | 99 | 31 | 8.1 |
| 3 |  | 59 | 90 | 64 | 13.3 |
| 4 |  | 72 | 98 | 38 | 8.3 |
| 5 |  | 63 | 95 | 57 | 12.4 |
| 6 |  (*trans*) | 62 | 99 (*1S,2R*) | 62 (*1R,2S*) | 21.0 |

**Table 4.** Kinetic resolution of racemic *N*-acyl-1,2-aminoalcohols using $Ac_2O$ and peptide catalyst **139**

| Entry | (*rac*)-Substrate | Temp/°C] | Conv./% | $k_{rel}$ |
|---|---|---|---|---|
| 1 |  | 4 | 47 | 20 |
| | | -23 | 37 | 40 |
| 2 |  | 4 | 52 | 22 |
| | | -23 | 48 | >50 |
| 3 |  | 4 | 54 | 15 |
| | | -23 | 40 | 32 |
| 4 |  | 4 | 47 | 14 |
| | | -23 | 35 | 40 |
| 5 |  | 4 | 51 | 20 |
| | | -23 | 38 | 39 |
| 6 |  | 4 | 51 | 9 |
| | | -23 | 35 | 19 |

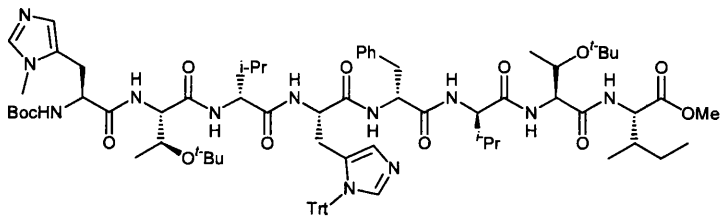



139

Figure 38.

Miller et al. have employed an alternative biomimetic approach to the identification of enantioselective *O*-acylation catalysts based on β-turn peptide fragments with defined secondary structures that contain nucleophilic *N*-alkyl-imidazole residues.[110] Initial work was directed towards the kinetic resolution of racemic *N*-acyl-1,2-aminoalcohols (Table 4) (to afford recovered (*S*)-alcohols) which were chosen due to their ability to hydrogen bond to a chiral peptide catalyst **139** (Fig. 38) that contained a D-Pro residue known to induce β-turns into peptide backbones.[111] Subsequent application of the full power of combinatorial synthesis for the preparation of 1st and 2nd generation libraries that contained over 100,000 and 600 peptide catalysts, respectively, resulted in the identification of octapeptide **140** (Fig. 39) that catalysed the resolution of more conventional secondary alcohol substrates in excellent e.e. (Table 5).[112]

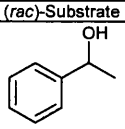
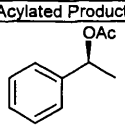
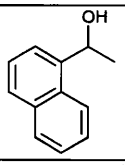
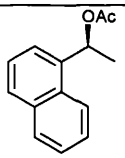
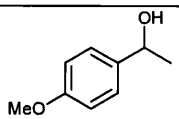
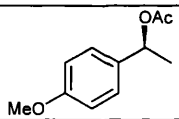
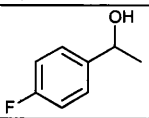
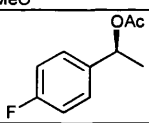
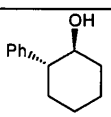
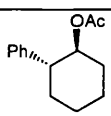
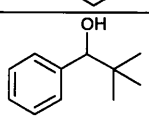
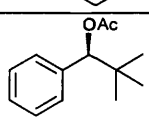
The potential use of this combinatorial approach for catalyst design was demonstrated in the asymmetric synthesis of (−)-Mitosane **143**, where an *N*-methyl-Histidine containing peptide **141** (Fig. 40) was isolated as the most active enantioselective catalyst from a library of 152 members for the resolution of allylic alcohol (*rac*)-**142** (Scheme 44).[113] The mechanism of this class of peptidic acyl transfer catalyst is currently under investigation using a novel approach that employs peptidic isosteres as mechanistic probes.[114]

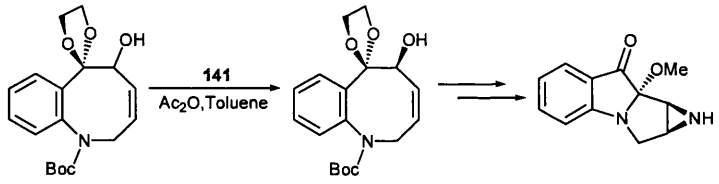



140

Figure 39.

Table 5. Kinetic resolutions catalysed by peptide **140** and $Ac_2O$

| Entry | (*rac*)-Substrate | Acylated Product | $k_{rel}$ |
|---|---|---|---|
| 1 |  |  | 20 |
| 2 |  |  | >50 |
| 3 |  |  | 16 |
| 4 |  |  | 11 |
| 5 |  |  | >50 |
| 6 |  |  | 30 |




**Scheme 44.** Synthesis of (–)-Mitosane **143** via kinetic resolution of (*rac*)-**142**.

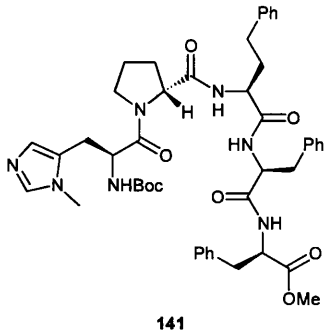



**Figure 40.**

The use of catalytic Lewis acids for the kinetic resolution of racemic alcohols has been less well explored, however a recent report has described on the potential of chiral yttrium–salen complex (*S,S*)-**144** (Fig. 41) for enantioselective acyl transfer.[115] The *s* values (1.50–4.81) obtained using these catalysts for resolution of a typical range of benchmark secondary alcohols **145a–e** are currently inferior to those obtained using chiral nucleophilic catalysts however, with the best results being obtained for indan-1-ol (*rac*)-**145c** which afforded recovered alcohol (*R*)-**145c** in 91% e.e. at 76% conversion (Table 6).

The development of a novel method for mono-benzylation of vicinal diols using dimethyltin dichloride and aqueous potassium carbonate that is proposed to proceed via an stannylene acetal intermediate has been exploited for the partial kinetic resolution of a range of 1-aryl-1,2-diols (*rac*)-**147a–e**. Thus, mono-benzoyl esters (*S*)-**148a–e** were obtained in moderate e.e. using

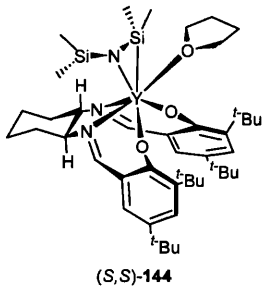
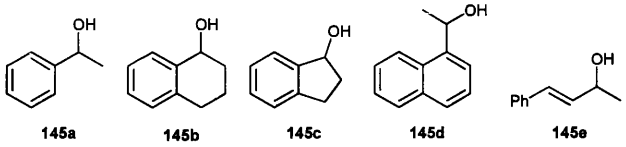



**Figure 41.**

**Table 6.** Kinetic resolution of secondary alcohols (*rac*)-**145a–e** catalysed by (*S,S*)-**144** via acylation with isopropenyl acetate




| Alcohol | *C* (%) | E.e. (%) recovered alcohol |
|---|---|---|
| **145a** | 65 | 23 (*S*) |
| **145b** | 39 | 14 (*R*) |
| **145c** | 76 | 91 (*R*) |
| **145d** | 61 | 36 (*S*) |
| **145e** | 42 | 13 (*S*) |

dibromobinaphthylstannepin (*S*)-**146** (Fig. 42) as a chiral catalyst (Scheme 45).[116]

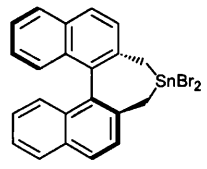
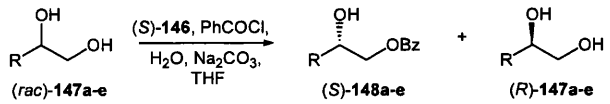



**Figure 42.**



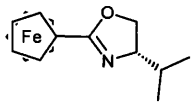

**a:** R=Ph
**b:** R=β-naphthyl
**c:** R=α-naphthyl
**d:** R=$CH_3(CH_2)_9$-
**e:** R=$C_2H_5$-

**148a:** 86% e.e., 38% yield
**148b:** 64% e.e., 25% yield
**148c:** 72% e.e., 41% yield
**148d:** 59% e.e., 35% yield
**148e:** 44% e.e., 35% yield

**Scheme 45.** Kinetic resolution of (*rac*)-**147a–e** catalysed by dibromobinaphthylstannepin (*S*)-**146**.

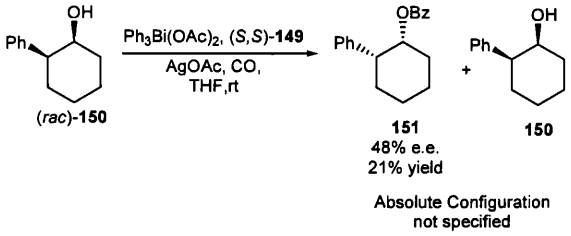
Uemura et al. have reported an alternative Pd(0) mediated carbonylation strategy for the kinetic resolution of racemic secondary alcohols involving treatment with carbon monoxide, $Ph_3Bi(OAc)_2$, AgOAc,

and a catalytic amount of $PdCl_2$ in the presence of homochiral oxazolinylferrocenyl phosphine ligand (*S*,*S*)-**149** (Fig. 43).[117] The enantioselectivity obtained in these type of resolutions were generally unsatisfactory however, with the best results to date being obtained for the resolution of *cis*-1-phenyl-hexan-2-ol (*rac*)-**150** to afford benzoate ester *cis*-**151** in 48% e.e. (Scheme 46).




(*S*,*S*)-**149**

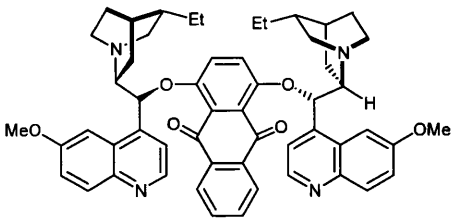
**Figure 43.**




**Scheme 46.** Kinetic resolution of *cis*-1-phenyl-hexan-2-ol (*rac*)-**150**.

## 6. Kinetic resolution via alcoholysis of racemic carbonyl derivatives

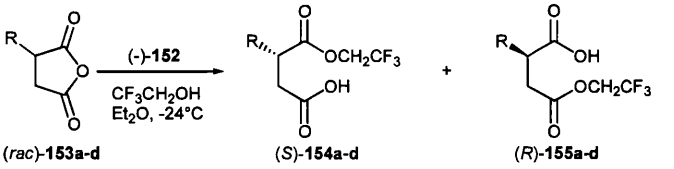
Deng et al. have recently published a series of important papers on the use of modified cinchona alkaloid catalysts for the kinetic resolution of racemic succinic anhydrides, 5-substituted-1,3-dioxolane-2,4-diones, and *N*-carbamoyl-α-aminoacid-*N*-carboxyanhydrides.




(-)-**152**

**Figure 44.**

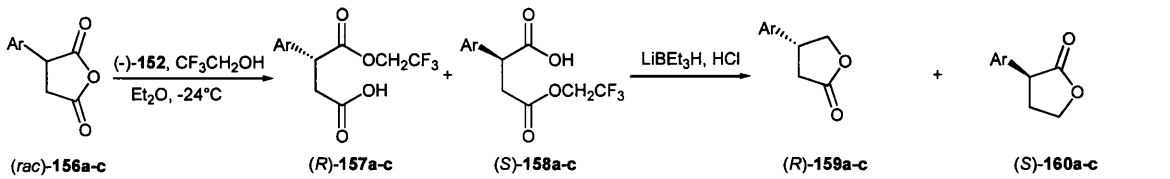
Building on their original work on the desymmetrisation of (*meso*)-cyclic anhydrides,[118] they reported that cinchona catalyst $(DHQD)_2AQN$ (–)-**152** (Fig. 44) could be employed as a catalyst for the parallel kinetic resolution of 2-alkyl succinic anhydrides (*rac*)-**153a–d** using trifluoroethanol (10 equiv.) as a nucleophile.[119] They found that the (*S*)-**153a–d** enantiomers of these 2-alkyl-succinic anhydrides were stereoselectively transformed into the corresponding trifluoroethyl 3-alkyl-succinates (*S*)-**154a–d**, whilst their (*R*)-**153a–d** enantiomers were converted into the corresponding trifluoroethyl 2-alkyl-succinates (*R*)-**155a–d**, affording easily separable regioisomeric products in excellent e.e. (Scheme 47). This methodology was extended to the kinetic resolution of 2-aryl-succinates (*rac*)-**156a–c** containing both electron-rich or electron-poor aryl substituents, enabling the synthetically useful lactones (*R*)-**159a–c** (via (*R*)-**157a–c**) and (*S*)-**160a–c** (via (*S*)-**158a–c**) to be obtained (Scheme 48). This approach clearly demonstrates the power of the strategy of parallel kinetic resolution for asymmetric




(*rac*)-**153a-d** (*S*)-**154a-d** (*R*)-**155a-d**

| | | |
|---|---|---|
| **a**: R=Me | **154a**: 93% e.e., 36% yield | **155a**: 80% e.e., 41% yield |
| **b**: R=Et | **154b**: 91% e.e., 38% yield | **155b**: 70% e.e., 50% yield |
| **c**: R=$^{n}C_8H_{17}$ | **154c**: 98% e.e., 38% yield | **155c**: 66% e.e., 41% yield |
| **d**: R=-$CH_2CH{=}CH_2$ | **154d**: 96% e.e., 40% yield | **155d**: 82% e.e., 49% yield |

**Scheme 47.** $(DHQD)_2AQN$ (–)-**152**-catalysed parallel kinetic resolution of (*rac*)-**153a–d**.



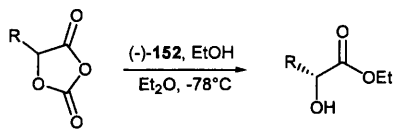

(*rac*)-**156a-c** (*R*)-**157a-c** (*S*)-**158a-c** (*R*)-**159a-c** (*S*)-**160a-c**

| | | | | |
|---|---|---|---|---|
| **a**: Ar=Ph | **157a**: 95% e.e. | **158a**: 87% e.e., | **159a**: 95% e.e., 44% yield | **160a**: 82% e.e., 32% yield |
| **b**: Ar=3-$C_6H_4$ | **157b**: 96% e.e. | **158b**: 83% e.e., | **159b**: 95% e.e., 45% yield | **160b**: 83% e.e., 30% yield |
| **c**: Ar=4-$ClC_6H_4$ | **157c**: 96% e.e. | **158c**: 76% e.e., | **159c**: 96% e.e., 44% yield | **160c**: 63% e.e., 29% yield |

**Scheme 48.** Asymmetric synthesis of β-aryl-lactones (*R*)-**159a–c** and α-aryl-γ-lactones (*S*)-**160a–c** via PKR of (*rac*)-**156a–c**.

synthesis, with the authors commenting that '*a conventional kinetic resolution of a selectivity factor of at least 112 would be required to obtain lactone* ***159c*** *from racemic anhydride (rac)-****156c*** *with the same e.e. and yield afforded by the parallel kinetic resolution processes.*'[120]

This methodology was further applied to the dynamic kinetic resolution of 5-aryl-1,3-dioxolane-2,4-diones (*rac*)-**161a–e** to afford α-hydroxy acids (*R*)-**162a–e** in >90% e.e. and >65% yield. The catalytic cinchona alkaloid catalyst (–)-**152** in these reactions was proposed to serve a dual function by facilitating efficient in situ racemisation of (*rac*)-**161a–e**, as well as acting as an efficient catalyst for alcoholytic kinetic resolution (Scheme 49). Related racemic 5-alkyl-1,3-dioxolane-2,4-diones did not undergo dynamic kinetic resolution under these conditions, presumably due to the reduced acidity of the α-proton at the C-5 stereocentre, however efficient kinetic resolutions were still observed in these cases with *s*-values >49.[121]




**a:** R=Ph, **162a:** 95% e.e., 71% yield
**b:** R=4-Cl-$C_6H_4$ **162b:** 96% e.e., 70% yield
**c:** R=4-Br-$C_6H_4$ **162c:** 96% e.e., 80% yield
**d:** R=4-F-$C_6H_4$ **162d:** 95% e.e., 65% yield
**e:** R=3,4-$F_2$-$C_6H_3$ **162e:** 94% e.e., 65% yield

**Scheme 49.** DKR of 5-aryl-1,3-dioxolane-2,4-diones (*rac*)-**161a–e**.

A third report on the use of $(DHQD)_2AQN$ (–)-**152** for the kinetic resolution of *N*-urethane-α-amino acid-*N*-carboxyanhydrides (UNCAs) (*rac*)-**163a–f** using methanol (0.5 equiv.) as a nucleophile at temperatures <–60°C was equally impressive, affording either enantiomer of the *N*-carbamoyl-α-amino acid in high e.e. Thus, UNCAs (*rac*)-**163a–f** that contained α-alkyl, α-benzyl, or α-aryl substituents were resolved in high e.e. using catalyst (–)-**152**, to afford *N*-carbamoyl-α-amino esters (*R*)-**164a–f**, and recovered UNCAs (*S*)-**163a–f** with *s* values ranging from 23 to 170. The recovered UNCAs (*S*)-**163a–f** were easily deprotected to their parent (*S*)-*N*-carbamoyl-α-amino acids **165a–f** via mild aqueous hydrolysis (Scheme 50). A general base-catalysed mechanism was proposed to explain the high stereoselectivities in these resolutions, in which coordination of the incipient alcohol nucleophile to a nitrogen atom of a dihydroquinidyl group of the catalyst results in a chiral complex that could efficiently discriminate between the two enantiomers of the racemic UNCAs as depicted in Figure 45.[122]

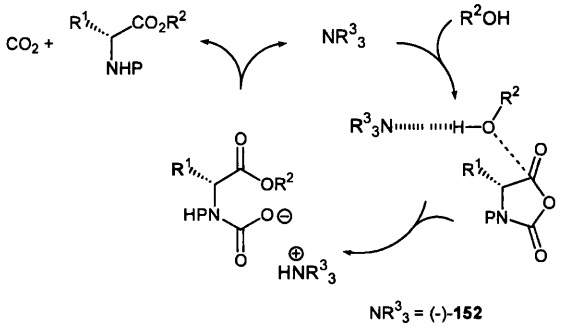
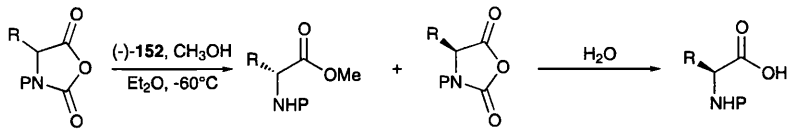


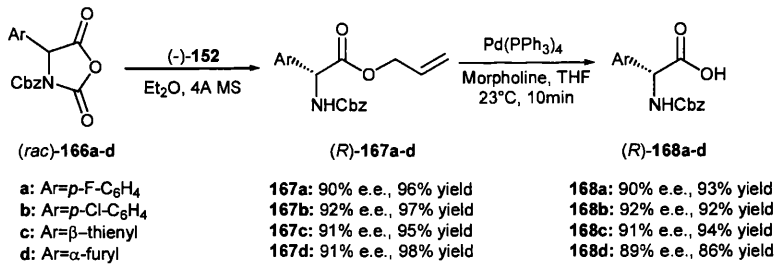

**Figure 45.** General base catalysis for (–)-**152**-catalysed alcoholysis of the (*R*)-enantiomer of UNCAs **163a–f**.

Subsequent investigations into the resolution of α-aryl-UNCAs (*rac*)-**166a–d** revealed that raising the temperature of the reaction mixture to 23°C, and substituting allyl alcohol for methanol as nucleophile, resulted in an efficient dynamic kinetic resolution at room temperature, thus affording a wide range of *N*-carbamoyl-α-aryl-α-amino esters including (*R*)-**167a–d** in >90% e.e. and >94% yield which were easily deprotected to their *N*-carbamoyl-α-amino acids (*R*)-**168a–d** under mild conditions (Scheme 51).[123]




**a:** R=$CH_2Ph$, P=Cbz **163a:** 93% e.e., 48% yield **165a:** 98% e.e., 48% yield
**b:** R=2-thienylmethyl, P=Cbz **163b:** 94% e.e., 49% yield **165b:** 95% e.e., 47% yield
**c:** R=Ph, P=Cbz **163c:** 97% e.e., 45% yield **165c:** 84% e.e., 46% yield
**d:** R=$CH_2Ph$, P=Fmoc **163d:** 92% e.e., 50% yield **165d:** 96% e.e., 47% yield
**e:** R=$CH_2CH_2Ph$, P=Alloc **163e:** 81% e.e., 53% yield **165e:** 96% e.e., 41% yield
**f:** R=*p*-$OMeC_6H_4$, P=Cbz **163f:** 74% e.e., 56% yield **165f:** 95% e.e., 43% yield

**Scheme 50.** Kinetic resolutions of UNCAs (*rac*)-**163a–f** via (–)-**152**-catalysed alcoholysis.




**Scheme 51.** DKR of 5-aryl-UNCAs (*rac*)-**166a–d** catalysed by (–)-**152**.

## 7. Resolution via palladium-catalysed allylic substitution reactions

There continues to be considerable interest in the development of methodology based on palladium-catalysed dynamic kinetic resolution of allylic acetates/carbonates/epoxides using a wide range of nucleophiles.[124] Recent reports in this area may be conveniently divided into those that apply existing chiral phosphine ligands to new substrates or transformations, and those directed towards the development of new classes of chiral ligand. Trost et al. have published detailed full experimental details on the use of their bis-phosphine ligand (*R,R*)-**169** (Fig. 46) for the dynamic kinetic resolution (or dynamic kinetic asymmetric transformation) of allylic mono-epoxide (*rac*)-**170** using phthalimide **171** as a nucleophile to afford (*R*)-**172** which was used for the asymmetric synthesis of the drugs vigabatrin (*R*)-**173** and ethambutol (*S,S*)-**174** (Scheme 52).[125] The alternative use of either enantiomer of ligand **175** (Fig. 47) to control the addition of benzoic acid, or the sodium salt of phenylsulfonylnitromethane to (*rac*)-**176** was also described thus enabling the preparation of (+)-**177** and **179**, as synthons for the synthesis of the aminocyclitol fragment of Hygromycin A **178**, and (–)-Cyclophellitol **180**, respectively (Scheme 53).[126]

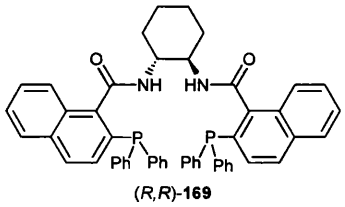



**Figure 46.**

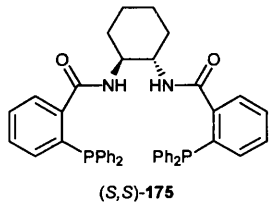
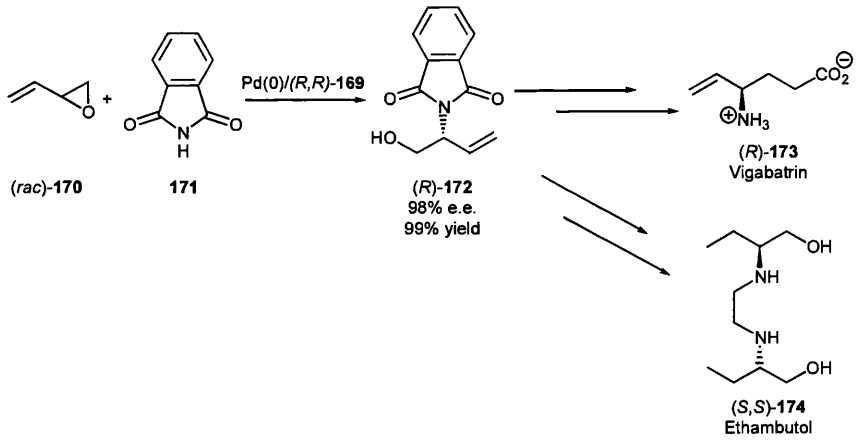
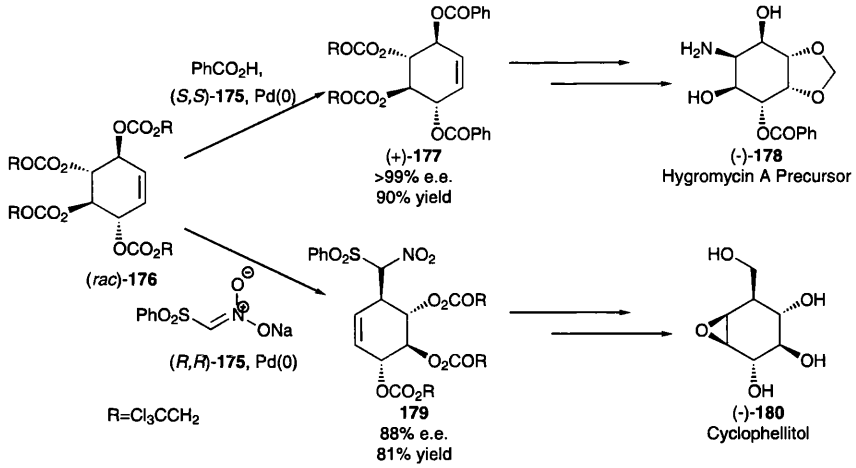



**Figure 47.**



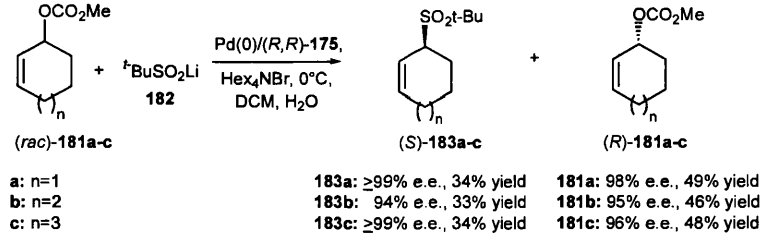

**Scheme 52.** Synthesis of Vigabatrin (*R*)-**173** and Ethambutol (*S,S*)-**174** via DKR.



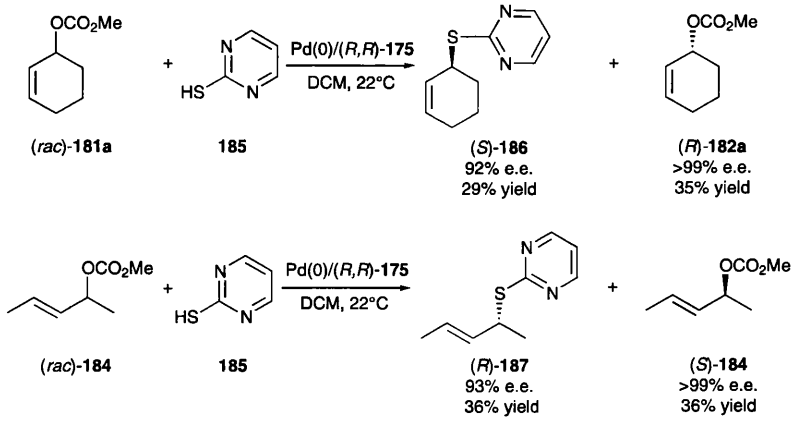

**Scheme 53.** Synthesis of Hygromycin A precursor **178** and (−)-Cyclophellitol **180** via DKR.

Building on their previous work on the Pd-catalysed asymmetric synthesis of allylic *S*-derivatives via kinetic resolution,[127] Gais et al. have reported the use of ligand (*R*,*R*)-**175** for the efficient kinetic resolution of both cyclic and acyclic carbonates (*rac*)-**181a–c** and (*rac*)-**184** using lithium *tert*-butyl sulfinate **182** (Scheme 54) or thiol **185** as nucleophiles affording allylic sulfones (*S*)-**183a–c** and allylic sulfides (*R*)-**186** and (*S*)-**187**, respectively with $s > 40$ (Scheme 55).[128]

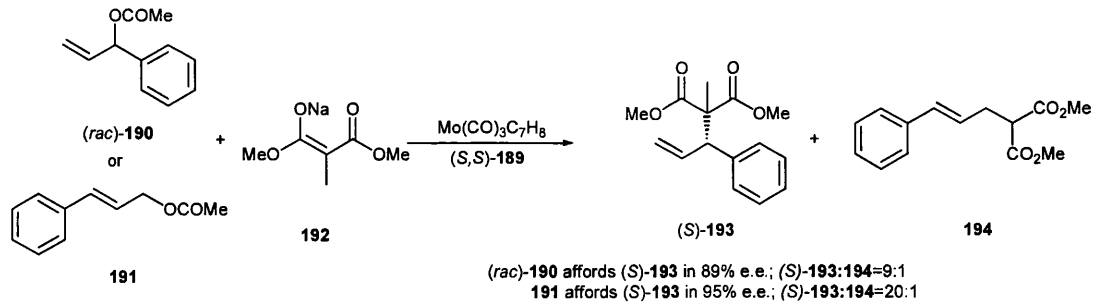
In a novel approach to the identification of new chiral ligands for asymmetric catalysis, Lloyd-Jones et al.




**Scheme 54.** Pd(0)-catalysed kinetic resolution of carbonates (*rac*)-**181a–c** with lithium *tert*-butyl sulfinate.




**Scheme 55.** Pd(0)-catalysed kinetic resolution of carbonates (*rac*)-**181a** and (*rac*)-**184** with thiol **185**.




**Scheme 56.** DKR of allylic carbonates (*rac*)-**190** and **191** via Mo allylic substitution.

have introduced the concept of screening catalysts derived from racemic ligands against scalemic substrates under pseudo zero order conditions. Thus, by monitoring the change in enantiomeric excess of a scalemic sample of cyclohexenyl acetate in palladium-catalysed allylic alkylation reactions using racemic bis-phosphine ligands over time, they were able to identify that the Trost-like ligand (*rac*)-**188** was an excellent prospective ligand for this class of kinetic resolution. Subsequent preparation of (*R*,*R*)-**188** (Fig. 48) in enantiomerically pure form, and its use as a chiral ligand for the palladium-catalysed resolution of racemic cyclohexenyl acetate, resulted in an *s* value >100 which is the highest value reported to date for this class of resolution.[129]

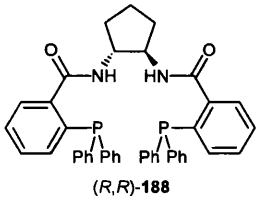



**Figure 48.**

From a practical perspective the process group at Merck have described a detailed mechanistic investigation into the alternative use of molybdenum-catalysed asymmetric allylic alkylation reactions using (bis)-picolinamide (*S*,*S*)-**189** (Fig. 49) as a ligand to induce enatioselectivity.[130] Thus, they have shown that the molybdenum-catalysed allylic alkylation of branched carbonate (*rac*)-**190** or unbranched carbonate **191** with a malonate nucleophile **192** results in efficient dynamic kinetic asymmetric transformation with a significant chiral memory effect,[131] to

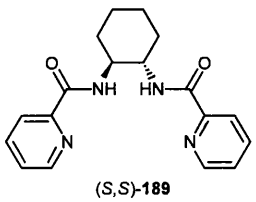



**Figure 49.**

afford the desired branched product (*S*)-**193** in good yields and e.e., with excellent selectivity over unbranched alkylation product **194** in both cases (Scheme 56).[132]

In 2000, Zhang et al. reported the development of a new phosphinoferrocenyl ligand (*S*,*S*)-**195** (Fig. 50) which was successfully employed for alkylation of 2-cyclohexenyl acetate (*rac*)-**196** via treatment with dimethyl malonate, *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and CsOAc.[133] This approach afforded the unreacted enantiomer (*S*)-**196** in 99% e.e. at 54% conversion (Scheme 57).

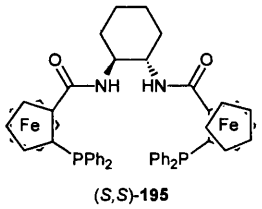
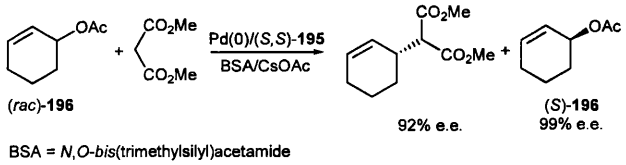
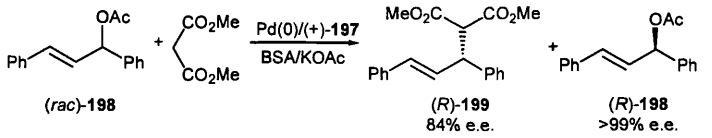



**Figure 50.**




**Scheme 57.** Kinetic resolution of 2-cyclohexenyl acetate (*rac*)-**182a** via Pd(0) allylic substitution.

Reetz et al. have described the use of a chiral helical diphosphine 2,15-bis-(diphenylphosphino)-hexahelicene (+)-**197** (Fig. 51) as a ligand in palladium-catalysed kinetic resolution of 1,3-diphenylpropenylacetate (*rac*)-**198** using dimethyl malonate, BSA and a catalytic amount of anhydrous KOAc. A conversion of 81% was observed after 1 h leading to the formation of the allylic substitution product (*R*)-**199** in 84% e.e. and unreacted 1,3-diphenylpropenylacetate (*R*)-**198** in >99% e.e. (Scheme 58).[134]




**Scheme 58.** Kinetic resolution of 1,3-diphenylpropenylacetate (*rac*)-**198** via Pd(0) allylic substitution.

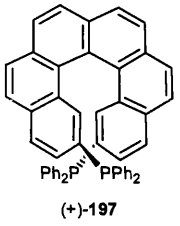



**Figure 51.**

A method related to parallel kinetic resolution is regiodivergent kinetic resolution, in which the enantiomers of a racemic substrate react with a chiral catalyst to afford regioisomeric products.[135] A proof of principle of this RKR approach was demonstrated for the palladium-catalysed allylic substitution of a mixture of all four possible stereoisomers of 5-vinyloxazolidinone (*rac*)-**201** and (*rac*)-**202** with phthalimide.[136] In this case the racemic mixture of diastereoisomers was treated with a Pd(0)-DIOP-(*R*,*R*)-**200** (Fig. 52) catalyst and phthalimide to afford (via diastereoisomeric Pd–allyl complexes **203** and **204**) a 1:1.2 mixture of vicinal diamine (*R*,*R*)-**205** (52% e.e., 33% yield) and 1,4-diamine (*S*)-**206** (48% e.e., 39% yield), respectively (Scheme 59).

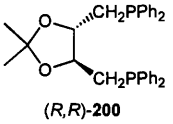
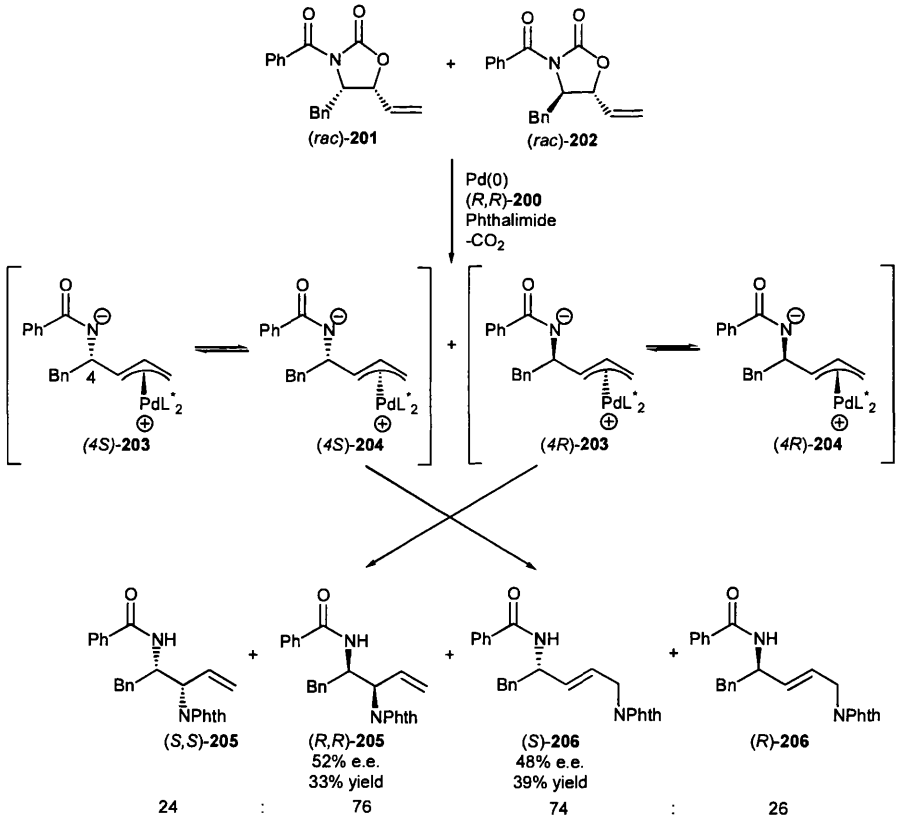
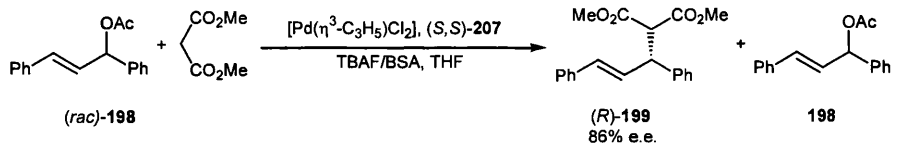



**Figure 52.**

Alternative types of chiral *P*,*O*-ligands have also been introduced that afford useful levels of stereocontrol for palladium-catalysed allylic substitution reactions. Firstly, Gilbertson et al. have employed combinatorial screening approaches to identify chiral phosphines such as (*S*,*S*)-**207** (Fig. 53) for the efficient kinetic




**Scheme 59.** Regiodivergent kinetic resolution of oxazolidin-2-ones (*rac*)-**201** and (*rac*)-**202**.




**Scheme 60.** Pd(0)-mediated kinetic resolution of (*rac*)-**198** using ligand (*S,S*)-**207**.

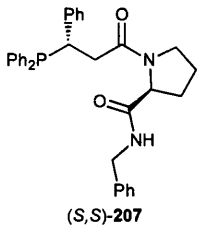



**Figure 53.**

resolution of allylic acetate (*rac*)-**198** to afford (*R*)-**199** in 86% e.e. at 45% conversion (Scheme 60).[137] Alternatively, a palladium complex derived from 3-(diphenylphosphino)butanoic acid (*S*)-**208** (Fig. 54) has been employed for the transformation of *cis*-alkenediol diacetate (*meso*)-**209** to afford mono-acetate (1*R*,4*S*)-**210** in 92% e.e. and 41% yield.[138] In this approach, initial desymmetrisation of (*meso*)-**209** to afford (1*R*,4*S*)-**210** and (1*S*,4*R*)-**210** is followed by a subsequent kinetic resolution step in which (1*S*,4*R*)-**210** is stereoselectively converted into the bis-alkylated product (1*R*,4*R*)-**211** (Scheme 61).[139]

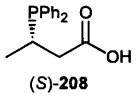



**Figure 54.**

## 8. Transition metal-mediated carbon–carbon bond forming reactions

The use of ruthenium and molybdenum catalysts for ring closing metathesis (RCM) is now a well established strategy for the construction of a wide range of compounds that contain small, medium and large ring systems.[140] The development of asymmetric variants of these catalysts has enabled stereoselective RCM reactions to be developed, using either kinetic resolution, or enantioselective desymmetrisation strategies.[141] In 1996, Grubbs et al. reported the first example of an RCM mediated kinetic resolutions using chiral molybdenum alkylidene biphenyl-complex (*R,R*)-**212** (Fig. 55) as a catalyst for the resolution of racemic dienes in moderate to good e.e.[142] In their best example, treatment of diene (*rac*)-**213** with 2.0 mol% of (*R,R*)-**212** at 25°C resulted in stereoselective cyclisation to afford allylic acetate (*R*)-**214**, enabling recovery of unreacted starting material (*S*)-**213** (10%) in 84% e.e. at 90% conversion (Scheme 62).

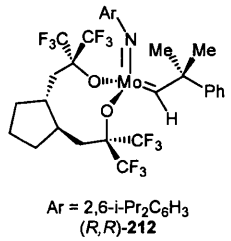
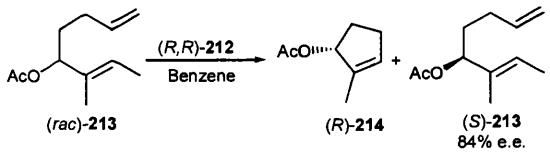
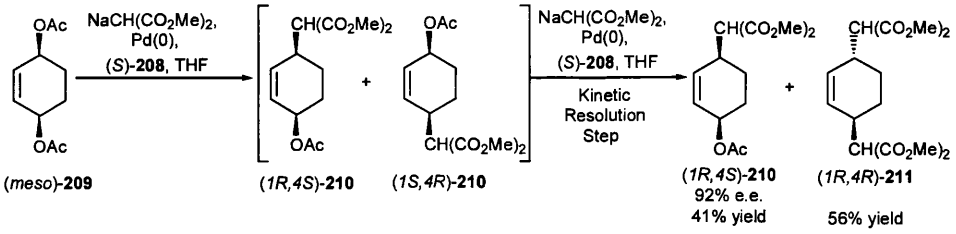



**Figure 55.**



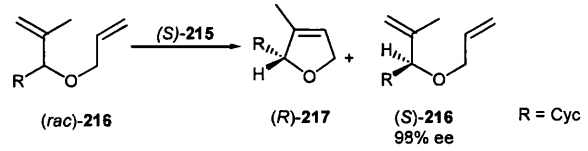

**Scheme 62.** Kinetic resolution using RCM catalysed by (*R,R*)-**212**.

Hexafluoro-MoTBEC catalyst (*R,R*)-**212** generally afforded only moderate levels of enantiodiscrimination for these type of kinetic resolutions however, and consequently Hoveyda et al. reported on a new improved Mo–biphen catalyst (*S*)-**215** (Fig. 56) for the catalytic resolution of a range of racemic allylic ethers.[143] In a typical reaction, treatment of allylic ether (*rac*)-**216** with 5 mol% of catalyst (*S*)-**215** in




**Scheme 61.** Sequential Pd(0)-mediated kinetic resolution of (*rac*)-**210** using ligand (*S*)-**208**.

toluene at −25°C gave dihydrofuran (*R*)-**217**, enabling recovery of unreacted (*S*)-**216** in 98% e.e. at 62% conversion (Scheme 63). Importantly, a recyclable polymer supported version of catalyst (*S*)-**215** has recently been reported that provides excellent selectivity for this type of kinetic resolution.[144]




**Scheme 63.** RCM kinetic resolution of an allylic ether (*rac*)-**216** catalysed by complex (*S*)-**215**.

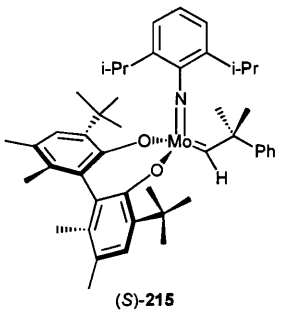
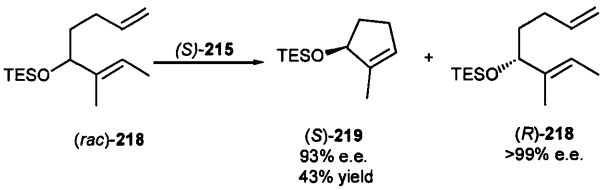



**Figure 56.**

Similar to Grubbs original work, Hoveyda et al. also described the use of catalyst (*S*)-**215** for RCM-catalysed kinetic resolution of racemic 1,6-dienes containing allylic alkoxy or allylic siloxy groups. For example, treatment of allylic triethylsilylether (*rac*)-**218** with catalyst (*S*)-**215** resulted in formation of TMS protected cyclopent-2-enol (*S*)-**219** in 93% e.e. and 43% yield, whilst unreacted (*R*)-**218** was recovered in >99% e.e. (Scheme 64).[145]




**Scheme 64.** Kinetic resolution of an acyclic diene (*rac*)-**218** catalysed by complex (*S*)-**215**.

RCM-catalysed kinetic resolution of structurally related racemic 1,7-dienes using (*S*)-**215** was ineffective however, and was best carried out using a new second generation Mo-BINOL catalyst (*R*)-**220** that gave outstanding selectivities for a range of racemic *O*-silyl-allylic ethers.[146] Interestingly, subsequent introduction of a third generation catalyst (*R*)-**221** (Fig. 57), that combines the structural features of both biphen-**215** and BINOL-**220**, has resulted in a robust catalyst that demonstrates an equally good reactivity profile for the resolution of both 1,6-dienes (*rac*)-**222** and 1,7-dienes (*rac*)-**223** (Table 7).[147]

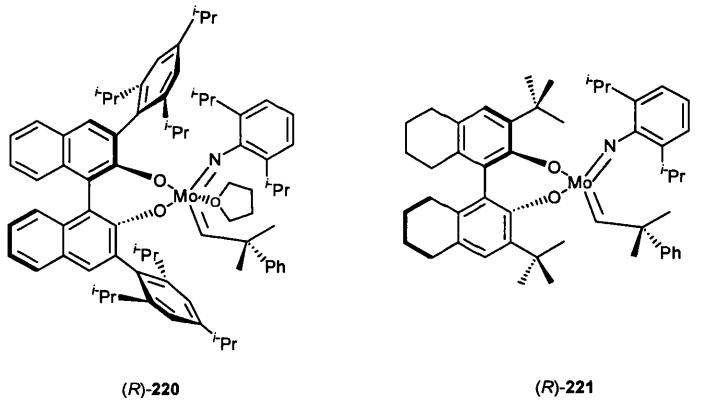
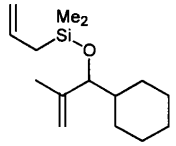
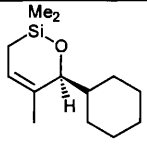
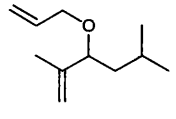
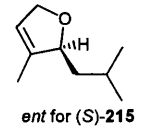
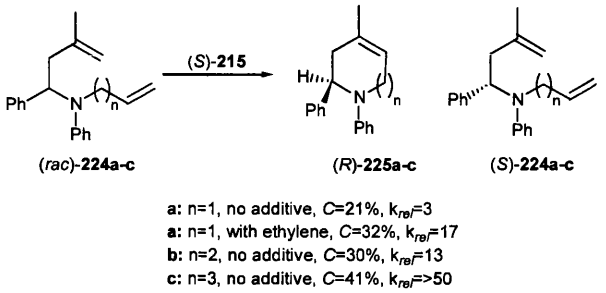



**Figure 57.**

**Table 7.** Mo-catalysed kinetic resolutions via RCM

| Substrate | Product | Catalyst | *C*/% | Dimer/% | $k_{rel}$ |
|---|---|---|---|---|---|
|  222 |  *ent* for (*S*)-**215** | (*S*)-**215** | 54 | 47 | <2.0 |
| | | (*R*)-**220** | 60 | 8 | >25 |
| | | (*R*)-**221** | 65 | 45 | >25 |
|  223 |  *ent* for (*S*)-**215** | (*S*)-**215** | 59 | <2 | 11 |
| | | (*R*)-**220** | 44 | <2 | <2.0 |
| | | (*R*)-**221** | 58 | <2 | 23 |

Finally, the use of biphen catalyst (*S*)-**215** has been extended to the kinetic resolution of unsaturated amines (*rac*)-**224a–c** containing 1,6-, 1,7- and 1,8-diene functionality for the synthesis of medium-ring unsaturated *N*-aryl amines (*R*)-**225a–c**, including an impressive stereoselective synthesis of (*R*)-**225c** ($n=3$) containing an eight-membered azocine skeleton (Scheme 65). These RCM reactions were carried out under essentially solvent free conditions, and in certain cases required the presence of one atmosphere of ethylene to ensure reversible Mo–alkylidene formation to ensure efficient enantiodiscrimination.[148]




**Scheme 65.** Kinetic resolution of acyclic amines (*rac*)-**224a–c** via RCM.

Schmalz et al. have reported the stereoselective functionalisation of dichloroarene–$Cr(CO)_3$ complex **227** via a Pd(0)-catalysed carbonylation reaction using Hayashi's PPF–pyrrolidine ligand (*R,S*)-**226** (Fig. 58) to control enantioselectivity. Thus, treatment of complex **227** with carbon monoxide, $Et_3N$, and 2 mol% of catalyst (*R,S*)-**226** in methanol resulted in the formation of chloroester (*S*)-**228** in 95% e.e. and 31% yield, as well as a 48% yield of bis-ester **229**. Subsequent investigations revealed that the e.e. of recovered chloroester (*S*)-**228** increased as the reaction proceeded, consistent with a second kinetic resolution step operating to selectively convert the (*R*)-**228** enantiomer to (bis)-ester **229** (Scheme 66).[149]

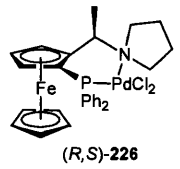
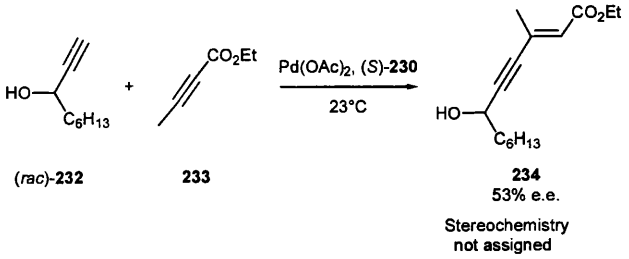



**Figure 58.**

Pfaltz et al. have disclosed that palladium complexes derived from chiral *P,N*-oxazoline ligands are highly efficient catalysts for the coupling of alkynes and alkenes, and have used this methodology for the kinetic resolution of racemic propargylic alcohols.[150] Thus, the use of *P,N*-ligand (*S*)-**230** resulted in the cross-coupling of propargylic alcohol (*rac*)-**232** with alkynoate **233** and to form (*E*)-ene-yne **234** in 53% e.e. (Scheme 67). The use of *P,N*-ligand (*S*)-**231** (Fig. 59) for the cross-coupling of γ-hydroxyalkynoate (*rac*)-**235** with alkyne **236** resulted in a 1:1 mixture of the regioisomeric butenolides **237** and **238** in 85% e.e. and 25% e.e., respectively (Scheme 68).




**Scheme 67.** Kinetic resolution of propargylic alcohol (*rac*)-**232**.

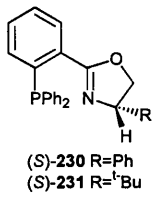
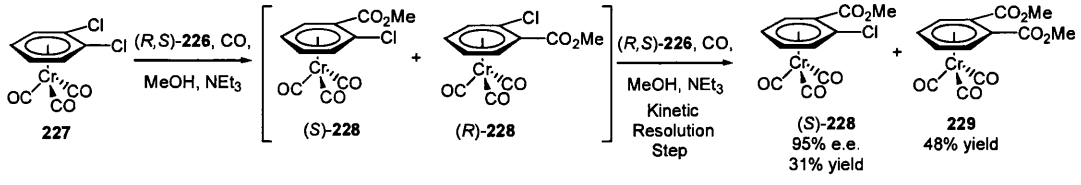
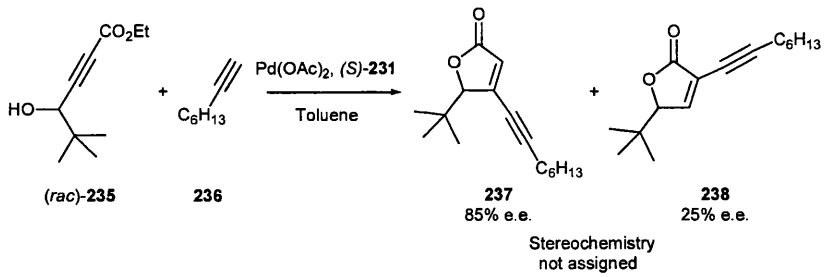



**Figure 59.**

Fu et al. have applied their recently published methodology[151] employing rhodium-catalysed cyclisation of alkyne–aldehydes to afford cyclopenten-2-ones for the kinetic resolution of racemic 3-methoxy-alkyn-1-als with good stereocontrol.[152] They proposed that the presence of the 3-methoxy substituent within the alkyn-1-al substrate resulted in two-point complexation to the rhodium catalyst to afford a highly ordered transition state that enabled 3-methoxy-alkyn-1-als (*rac*)-**239a–f** to be resolved in ≥90% e.e. via enantioselective cyclisation of their (*S*)-enantiomers to afford cyclopent-2-enones (*S*)-**240a–f** (Table 8).

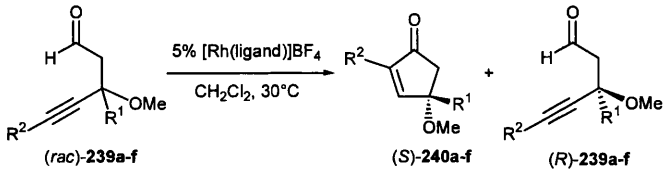



**Scheme 66.** Stepwise kinetic resolution of scalemic dichloroarene-$Cr(CO)_3$ complex **228** via a Pd(0)-catalysed carbonylation reaction.




**Scheme 68.** Kinetic resolution of α-hydroxyalkynoate (*rac*)-**235**.

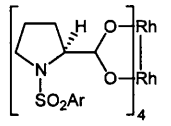
**Table 8.** Rhodium-catalysed kinetic resolution of 4-alkynals (*rac*)-**239a–f**




| Substrate | $R^1$ | $R^2$ | Ligand | *C* (%) | e.e. of (*R*)-**239a–f** | *s* |
|---|---|---|---|---|---|---|
| **239a** | H | Ph | (*S*,*S*)-$^i$Pr-DUPHOS | 56 | 93 | 22 |
| **239b** | H | *o*-Tol | (*S*,*S*)-$^i$Pr-DUPHOS | 56 | 90 | 19 |
| **239c** | H | $CH_2CH(CH_3)_2$ | (*S*,*S*)-$^i$Pr-DUPHOS | 53 | 93 | 41 |
| **239d** | $CH_3$ | Ph | (*R*)-Tol-BINAP | 60 | 99 | 22 |
| **239e** | $CH_3$ | *c*-Hex-1-enyl | (*R*)-Tol-BINAP | 63 | 99 | 18 |
| **239f** | $^i$Pr | Ph | (*R*)-Tol-BINAP | 76 | 95 (*S*) | 5.4 |

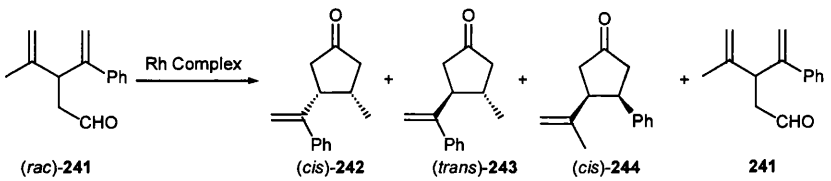
Rhodium-catalysed cyclisations have also been applied to the kinetic resolution of 3,4-disubstituted 4-pentenal (*rac*)-**241** using the cationic Rh[(*S*)-BINAP]$ClO_4$ complex which gave *trans*-**243** in >95% e.e. and 42% yield, and enantiomerically enriched **241** in 43% yield. The alternative use of neutral complex Rh[(*S*)-BINAP]Cl resulted in stereoselective cyclisation of (*rac*)-**241** to afford *cis*-**242** in >95% e.e. and 19% yield, and *cis*-**244** in >95% e.e. and 21% yield (Scheme 69).[153]

Davies et al. have employed their [$Rh_2$-DOSP] catalyst (*S*)-**245** (Fig. 60) for highly enantioselective and diastereoselective C–H insertion reactions into *N*-Boc-2-pyrrolidines substituted (*rac*)-**246a–d**, thus enabling the simultaneous control of three stereocentres in high e.e.[154] Reaction of methyl *p*-bromophenyldiazoacetate **247** with *N*-Boc-proline derived esters (*rac*)-**246a,b**, or protected alcohols (*rac*)-**246c,d**, in the presence of catalyst (*S*)-**245** resulted in the formation of (*trans*)-1,3-disubstituted-pyrrolidines (1*R*,4*S*,5*S*)-**248a–d** in >79% e.e., >78% d.e. and in >30% yield (Scheme 70).




Ar = *p*-($C_{12}H_{25}$)$C_6H_4$
(*S*)-**245**

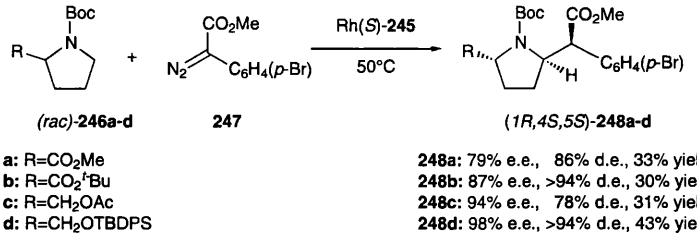
**Figure 60.**




Rh[(*S*)-BINAP]$ClO_4$: (*trans*)-**243**: >95% e.e., 42% yield; **241**: 43% yield
Rh[(*S*)-BINAP]Cl: (*cis*)-**242**: >95% e.e., 19% yield; (*cis*)-**244**: >95% e.e., 21% yield

Absolute stereochemistry of major products not assigned

**Scheme 69.** Kinetic resolution via asymmetric cyclisation of dissymmetric 3,4-disubstituted 4-pentenal (*rac*)-**241**.




**Scheme 70.** Kinetic resolution via enantioselective C–H insertion into 2-substituted pyrrolidines (*rac*)-**246a–d**.

## 9. Kinetic resolution via 1,4-conjugate addition[155]

Feringa et al. have continued to explore their original work employing chiral phosphoroamidite ligands[156] to control the stereoselective 1,4-addition of dialkylzinc species to conjugate acceptors, which has previously been reported for the kinetic resolution of 1,3-diene monoepoxides and alkynyl epoxides.[157] Recent developments have shown that enantioselective conjugate addition of 0.5 equiv. of $Et_2Zn$ to methylidenecyclohexene epoxide (*rac*)-**250**, in the presence of catalytic amounts of $Cu(OTf)_2$ and phosphoramidite ligand (*S,S,S*)-**249** (Fig. 61), resulted in a stereoselective $S_N2'$ reaction to afford allylic alcohol (*S*)-**251** in 88% e.e. and 45% yield (Scheme 71).[158] This methodology was further developed to afford a parallel kinetic resolution strategy, in which the use of excess $Et_2Zn$ in the presence of $Cu(OTf)_2$ and ligand (*R,R,R*)-**249** resulted in each enantiomer of mono-epoxide (*rac*)-**250** being stereospecifically and quantitatively transformed into allylic alcohol (*R*)-**251** (80% e.e., $S_N2'$), or homoallylic alcohol (*S,S*)-**252** (99% e.e., $S_N2$), respectively (Scheme 72).[159]

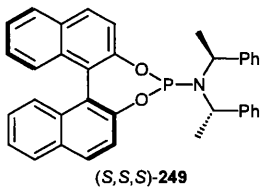
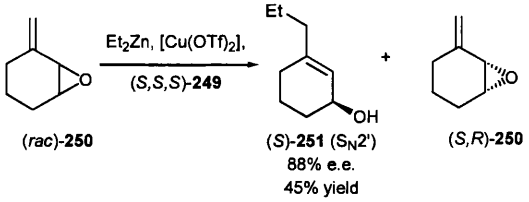
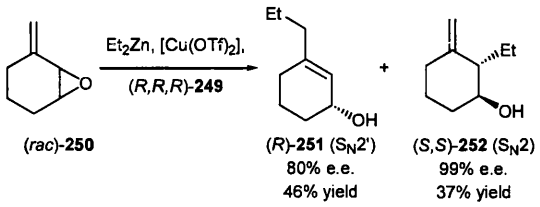



**Figure 61.**

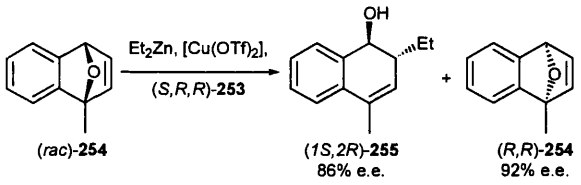



**Scheme 71.** Kinetic resolution of vinyl epoxide (*rac*)-**250** with (*S,S,S*)-**249**.

Additionally, they have also demonstrated that an oxabenzonorbornadiene derivative (*rac*)-**254** can be successfully resolved using this type of catalytic conjugate addition approach, with (*S,R,R*)-**253** (Fig. 62) catalysing the addition of $Et_2Zn$ to afford recovered cyclic ether (*R,R*)-**254** in 92% e.e., and (*anti*)-dihydronaphthol (1*S*,2*R*)-**255** in 86% e.e. at 56% conversion (Scheme 73).[160]




**Scheme 72.** PKR of a vinyl epoxide (*rac*)-**250** with (*R,R,R*)-**249**.




**Scheme 73.** Kinetic resolution of oxabenzonorbornadiene derivative (*rac*)-**254**.

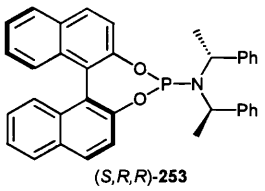
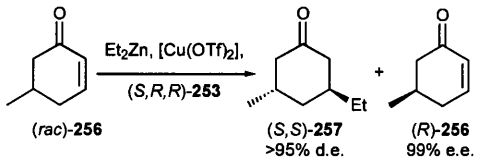


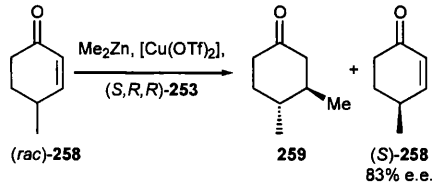

**Figure 62.**

In 2001, Feringa et al. also demonstrated that their copper–BINOL–phosphoramidite complex could also be used for the kinetic resolution of a range of racemic 5-alkyl cyclohex-2-enones via stereoselective 1,4-conjugate addition of a range of different $(R_1)_2Zn$ species ($R_1$ = Me, Et, $^i$Pr and $^n$Bu).[161] For example, treatment of 5-methylcyclo-hex-2-en-one (*rac*)-**256** with ligand (*S,R,R*)-**253**, $[Cu(OTf)_2]$, and diethyl zinc gave the unreacted enantiomer (*R*)-**256** in 99% e.e. and the *syn*-3,5-dialkyl addition product (*S,S*)-**257** in >95% d.e. at 53% conversion (Scheme 74). Indeed, the authors report that the stereoselectivities obtained in these transformations rivalled those of enzymatic-catalysed kinetic resolutions

since they *'approach the near perfect situation...as the reaction virtually ceases at 50% conversion in the presence of 1 equiv. of $Me_2Zn$'*. The resolution of 4-methyl-cyclohex-2-enone (*rac*)-**258** using (*S,R,R*)-**253** was also reported affording **259** (stereochemistry not assigned), and (*S*)-**258** in 83% e.e. at 55% conversion using $Me_2Zn$ as a nucleophile (Scheme 75).



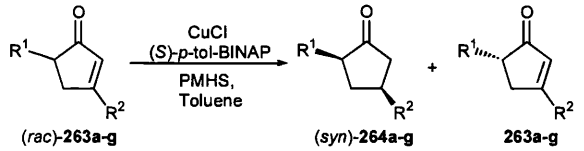

**Scheme 74.** Kinetic resolution of 5-methyl-2-cyclohex-2-enone (*rac*)-**256**.




**Scheme 75.** Kinetic resolution of 4-methyl-2-cyclohexanone (*rac*)-**258**.

Independent studies by Krause et al. have also shown that this kinetic resolution protocol also works equally well for racemic 6-*tert*-butyl-cyclohex-2-enone (*rac*)-**260** which on treatment with 0.8 equiv. of $Et_2Zn$ in the presence of ligand (*S,R,R*)-**253** resulted in conversion of the (*S*)-enantiomer to (*S,S*)-**262a** in 89% e.e. and the recovery of (*R*)-**260** in 82% e.e. after 42% consumption. The alternative use of $(n\text{-Bu})_2Zn$ as a nucleophile resulted in formation of (2*R*,5*S*)-**261b** and (2*S*,5*S*)-**262b** in a combined yield of 78%, with (*R*)-**260** being recovered in >99% e.e. (Scheme 76).[162]

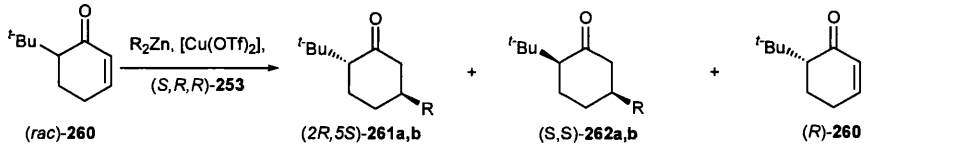
Buchwald et al. have employed a different strategy for the dynamic kinetic resolution of cyclic α,β-unsaturated ketones (*rac*)-**263a–g**, employing a chiral copper hydride species derived from CuCl, NaO$^t$Bu and (*S*)-*p*-tol-BINAP, for the catalytic 1,4-conjugate reduction of 3,5-dialkyl cyclopentenones using poly(methylhydrosiloxane) as a stoichiometric reductant.[163] Reduction of α,β-unsaturated ketones (*rac*)-**263a–g** using this chiral Cu–H–BINAP complex occurred with universally high *s* values to afford, affording *syn*-**264a–g** and unreacted chiral ketones **263a–g** in high e.e. (Scheme 77). Addition of NaO*t*-Bu/*t*-BuOH to the reaction media facilitated efficient racemisation at the $C_5$ stereocentre in situ, resulting in a DKR protocol that gave *syn*-2,5-dialkyl-cyclopentanones **264a–f** in >90% e.e and in high diastereoisomeric excess {<10% yield of *anti*-**265a–f** formed in all cases} (Scheme 78).




PMHS=polymethylhydrosilane

**a**: $R^1$=Me, $R^2$=$(CH_2)_2Ph$ — **263a**: 95% e.e.
**b**: $R^1$=$^i$Pr, $R^2$=$(CH_2)_2Ph$ — **263b**: 97% e.e.
**c**: $R^1$=$^t$Bu, $R^2$=$(CH_2)_2Ph$ — **263c**: 91% e.e.
**d**: $R^1$=$CH_2CO_2{}^t$Bu — **263d**: 95% e.e.
**e**: $R^1$=Bn, $R^2$=$^i$Pr — **263e**: 96% e.e.
**f**: $R^1$=Me, $R^2$=Ph — **263f**: 72% e.e.
**g**: $R^1$=$^n$Bu, $R^2$=$(CH_2)_2Ph$ — **263g**: 90% e.e.

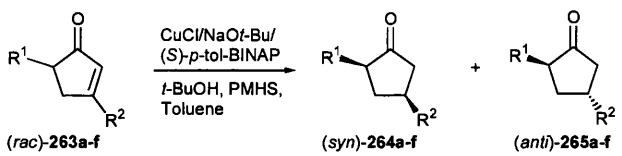
**Scheme 77.** Kinetic resolution of 3,5-dialkylcyclopent-2-enones (*rac*)-**263a–g**.




**a**: R = Et
**b**: R = $^n$Bu

**261b**: >99% e.e., 18% yield
**262a**: 89% e.e., 36% yield
**262b**: 60% yield
**260**: 82% e.e., 58% yield
**260**: >99% e.e., 22% yield

**Scheme 76.** Kinetic resolution of 6-*tert*-butyl-2-cyclohex-2-en-one (*rac*)-**260**.



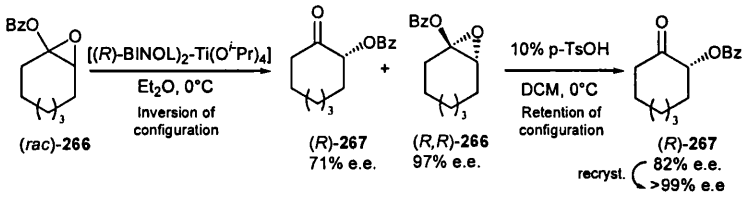

**a**: $R^1$=Me, $R^2$=$(CH_2)_2Ph$ — **264a**: 91% e.e., 82% d.e., 89% yield
**b**: $R^1$=$^i$Pr, $R^2$=$(CH_2)_2Ph$ — **264b**: 93% e.e., 86% d.e., 94% yield
**c**: $R^1$=$^t$Bu, $R^2$=$(CH_2)_2Ph$ — **264c**: 94% e.e., 87% d.e., 94% yield
**d**: $R^1$=$CH_2CO_2{}^t$Bu, $R^2$=$(CH_2)_2Ph$ — **264d**: 93% e.e., 80% d.e., 91% yield
**e**: $R^1$=Bn, $R^2$=$^i$Pr, 93% e.e. — **264e**: 93% e.e., 83% d.e., 95% yield
**f**: $R^1$=Me, $R^2$=Ph, 91% e.e. — **264f**: 91% e.e., 93% d.e., 90% yield

**Scheme 78.** Dynamic kinetic resolution of 3,5-dialkylcyclopent-2-enones **263a–f**.

## 10. Lewis acid- or base-catalysed kinetic resolution

In 2002, Shi et al. reported the chiral Lewis acid-catalysed resolution of racemic enol ester epoxides, which converted both enantiomers of (*rac*)-**266** into the same enantiomer of α-benzoyloxy ketone (*R*)-**267** (Scheme 79).[164] This was achieved by resolution of enol ester epoxide (*rac*)-**266** with a catalytic amount of the chiral Lewis acid [(BINOL)$_2$–Ti(O$^i$Pr)$_4$], to yield a mixture of the unreacted epoxide (*R,R*)-**266** in 97% e.e. and α-benzoyloxy ketone (*R*)-**267** in 71% e.e. which was formed via intramolecular benzoyl migration with inversion of configuration (Fig. 63, pathway a). This mixture was then treated with a catalytic amount of an achiral protic acid (pTSA) which catalysed the rearrangement of (*R,R*)-**266** via intramolecular benzoyl migration with retention of configuration (Fig. 63, pathway b) to afford α-benzoyloxy ketone (*R*)-**267** in an overall 82% e.e., which could be improved to >99% e.e. after recrystallisation.

Tu et al. have reported on a novel strategy for the enantioselective preparation of β-hydroxy ketones (*R,R*)-**269a–f** containing quaternary stereogenic centres via rearrangement of racemic tertiary α-hydroxy epoxides (*rac*)-**268a–f** using Ti–[(*R*)-BINOL]$_2$ complexes to catalyse enantioselective semipinacol rearrangements (Scheme 80).[165] The best enantioselectivities were observed for substrates in which the migrating group of the tertiary alcohol substrate was an aryl substituent, with tertiary α-hydroxy epoxides (*S,S*)-**268a–f** being recovered in 77–94% e.e. at 60–70% conversion.




**Scheme 79.** Enantioconvergent kinetic resolution of (*rac*)-**266** to afford the same enantiomer of α-benzoyloxy ketone (*R*)-**267**.

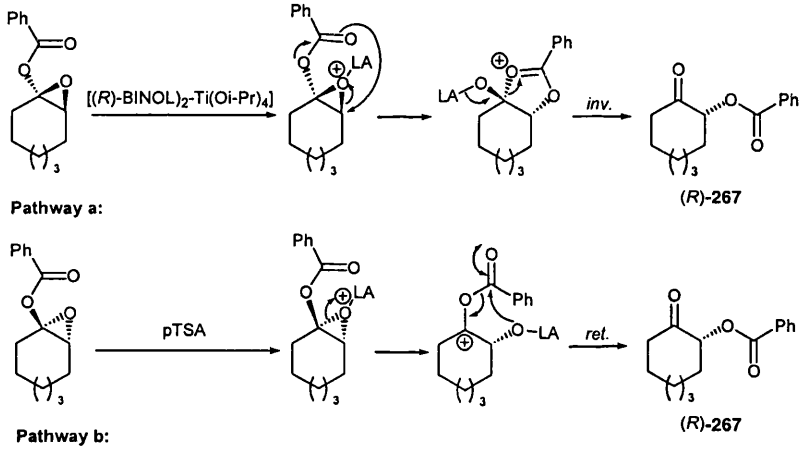
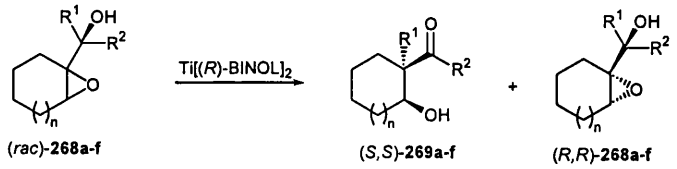



**Figure 63.** Two pathways for the rearrangement of each enantiomer of enol ester epoxide (*rac*)-**266** to afford (*R*)-**267**.

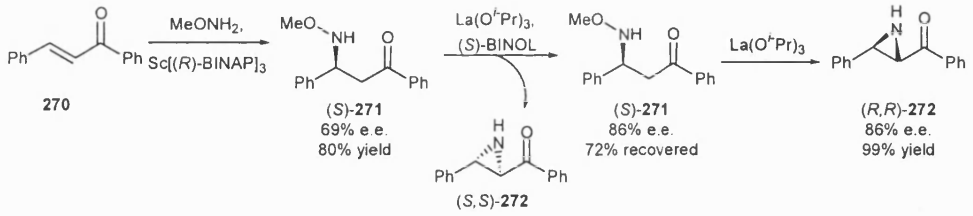



**a:** n=0, $R^1$=$R^2$=Ph, *C*=62
**b:** n=1, $R^1$=$R^2$=Ph, *C*=63
**c:** n=1, $R^1$=Bn, $R^2$=Ph, *C*=64
**d:** n=1, $R^1$=Ph, $R^2$=Bn, *C*=65
**e:** n=1, $R^1$=$^n$Bu, $R^2$=1-Naphth, *C*=65
**f:** n=1, $R^1$=$^n$Bu, $R^2$=*p*-$CF_3$Ph-, *C*=67

**269a:** 61% e.e.
**269b:** 60% e.e.
**269c:** 48% e.e.
**269d:** 47% e.e.
**269e:** 46% e.e.
**269f:** 41% e.e.

**268a:** 90% e.e.
**268b:** 94% e.e.
**268c:** 82% e.e.
**268d:** 80% e.e.
**268e:** 79% e.e.
**268f:** 77% e.e.

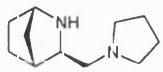
**Scheme 80.** Kinetic resolution of α-hydroxy epoxides (*rac*)-**268a–f** catalysed by Ti[(*R*)-BINOL]$_2$.




**Scheme 81.** Three-step enantioselective catalytic conversion of chalcone to afford α-keto aziridine (*R*,*R*)-**272**.

In 2002, Inanaga et al. described the synthesis of an enantiomerically enriched α-keto aziridine (*R*,*R*)-**272** via a protocol involving sequential action of three lanthanoid complexes including (i) Sc[(*R*)-BINAP]$_3$-catalysed Michael addition of *O*-methylhydroxylamine to chalcone **270** to afford β-amino-ester (*S*)-**271** in 69% e.e.; (ii) La(O$^i$Pr)$_3$–(*S*)-BINOL complex-mediated kinetic resolution of enantioenriched (*S*)-**271** to enhance its e.e. from 69 to 86% e.e. via preferential cyclisation of (*R*)-**271** to afford aziridine (*S*,*S*)-**272**; (iii) La(O$^i$Pr)$_3$-catalysed ring closure of (*S*)-**271** to afford aziridine (*R*,*R*)-**272** in 86% e.e. (Scheme 81).[166]

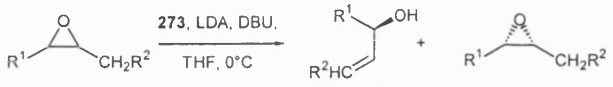
The majority of asymmetric deprotonation reactions reported to date involve protocols that require the use of stoichiometric amounts of chiral bases for efficient asymmetric induction;[167] however, Andersson et al. have recently introduced the use of 5 mol% of enantiopure diamine (1*S*,3*R*,4*S*)-**273** (Fig. 64) as a catalytic ligand for



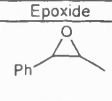
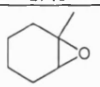
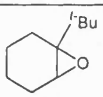
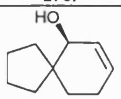
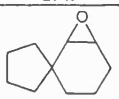
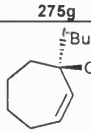
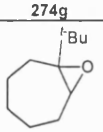
(1*S*,3*R*,4*R*)-**273**

**Figure 64.**

**Table 9.** Kinetic resolution of (*rac*)-**274a–h** via asymmetric deprotonation using a catalytic amount of chiral diamine (1*S*,3*R*,4*S*)-**273**




(*rac*)-**274a-h** **275a-h** **274a-h**

| Entry | Product | e.e./% | yield/% | Epoxide | e.e./% | yield/% |
|---|---|---|---|---|---|---|
| 1 |  **275a** | 89 | 94 |  **274a** | 85 | 84 |
| 2 |  **275b** | 63 | 87 |  **274b** | 79 | 94 |
| 3 |  **275c** | 79 | 34 |  **274c** | - | 50 |
| 4 |  **275d** | 94 | 40 |  **274d** | 87 | 38 |
| 5 |  **275e** | 99 | 40 |  **274e** | 99 | 36 |
| 6 |  **275f** | 94 | 43 |  **274f** | 99 | 47 |
| 7 |  **275g** | 90 | 45 |  **274g** | 93 | 40 |
| 8 |  **275h** | 94 | 34 |  **274h** | 41 | 51 |

the desymmetrisation of *meso*-epoxides in the presence of LDA as a stoichiometric base.[168] This methodology has now been extended to the kinetic resolution of both acyclic and cyclic epoxides to afford recovered chiral epoxides **274a–h** and chiral allylic alcohols **275a–h** with good levels of stereocontrol (Table 9).[169,170]

## 11. Conclusions

Over 125 reports on catalytic kinetic resolutions using non-enzymatic catalysts have appeared over the last three years based on the use of existing or new catalytic methodology, many of which produce chiral starting materials or products in very high e.e. Strategies such as HKR of racemic terminal epoxides, Sharpless epoxidation of allylic alcohols, and the use of transfer hydrogenation catalysts for oxidative/reductive resolution are now widely used for the preparation of synthons for natural product synthesis, whilst it is clear that the application of new types of stereoselective catalysts will provide new opportunities for kinetic resolution in the near future.

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# An (*E*)-selective synthesis of trisubstituted (*E*)-α,β-unsaturated acid derivatives†

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**Potassium alkoxides of *N*-acyloxazolidin-2-one derived *syn*-aldolates undergo a novel tandem intramolecular cyclisation elimination reaction to afford trisubstituted (*E*)-α,β-unsaturated amides in high d.e., which may be converted into their corresponding acids or oxazolines in good yield.**

There are currently few general methods available for the diastereoselective synthesis of (*E*)-α,β-unsaturated acids/esters/amides that are substituted at both their α- and β-positions.[1] These types of trisubstituted α,β-unsaturated acid derivatives are important targets because they serve as versatile substrates for a wide range of synthetic methodology,[2] and for the construction of a wide range of natural products.[3,4] Previously, (*E*)-acid derivatives of this type have been prepared using Wittig,[3] or Horner–Emmons[4] methodology, however alternative diastereoselective protocols employing excess $SmI_2$[5] or $CrCl_2$[6] to effect the reductive elimination of α-halo-β-hydroxy-esters or amides have recently been described. We now report an alternative approach towards this class of acid fragment, that employs *syn*-β-hydroxy-*N*-acyloxazolidin-2-ones as substrates for a novel intramolecular cyclisation/elimination reaction to afford trisubstituted (*E*)-α,β-unsaturated amides in high d.e.

In the course of our synthetic studies we prepared nine racemic *syn*-aldolates **2a–i** in high d.e. *via* reaction of the boron enolates of *N*-acyloxazolidin-2-ones **1a–d** (**1a** R = Me; **1b** R = $^i$Pr; **1c** R = Ph, **1d** R = $PhCH_2$–) with a series of aldehydes according to well established literature precedent.[7] It was found that treatment of these *syn*-aldolates **2a–h** with 1.5 equivalents of KHMDS in THF at −78 °C resulted in a clean elimination reaction to afford the corresponding α,β-unsaturated amides (*E*)-**3a–h** in 67–99% isolated yield, and in >90% d.e.[8] in all cases.[9] It is noteworthy that this simple elimination methodology is general in scope, with linear and branched R-substituents being tolerated at the α-position of the *syn*-aldolates **2a–h**, and with aliphatic, unsaturated, and aromatic (neutral and electron rich) $R_1$-substituents being tolerated at the β-position (Scheme 1, Table 1). The only limitation of this methodology occurred during elimination of **2i** (R = Ph, $R_1$ = Et) which gave **3i** in a lower 47% isolated yield as a result of a competing *retro*-aldol reaction which gave (*N*-phenylacetyl)oxazolidin-2-one **1c** (R = Ph) and propionaldehyde (not isolated) as competing side-products in 32% yield.

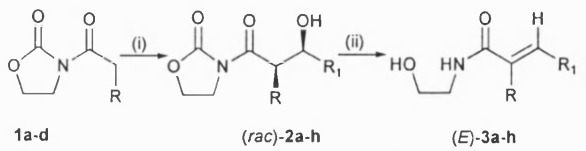
It is well known that sterically unhindered *N*-acyloxazolidin-2-ones can undergo endocyclic ring cleavage *via* either inter- or intramolecular attack of nucleophiles at their oxazolidin-2-one carbonyl groups.[10] Consequently, it was proposed that the high diastereoselectivities observed for the formation of (*E*)-α,β-unsaturated amides **3a–h** in this reaction could be explained by invoking an intramolecular endocyclic cleavage mechanism. Thus, potassium alkoxide **4** initially undergoes intramolecular attack at the oxazolidin-2-one carbonyl resulting in O–O carbonyl migration, to afford 1,3-oxazinane-2,4-dione alkoxide **5**. Subsequent anion equilibration of alkoxide **5** to enolate **6** would then enable stereoselective elimination of carbon dioxide to occur to afford the trisubstituted secondary amide (*E*)-**3** in high d.e. (Fig. 1).

It has been reported previously that reaction of the Zn enolate of α-bromo-*N*-acyl-oxazolidin-2-one **7** with benzaldehyde did not afford the expected aldolate product, but instead gave a mixture of rearranged 1,3-oxazinane-2,4-dione diastereoisomers **8** and **9** in good yield (Scheme 2).[11] Since this implied that Zn alkoxides of β-hydroxy-*N*-acyloxazolidin-2-ones underwent rearrangement to their corresponding 1,3-oxazinane-2,4-diones, we treated *syn*-aldolate **2f** with 10 mol% of $Et_2Zn$ in $CH_2Cl_2$ at room temperature to cleanly afford its corresponding 1,3-oxazinane-2,4-dione **10** in 88% yield.[12] Subsequent treatment of **10** with KHMDS in THF at −78 °C gave (*E*)-**3f** in >90% d.e., thus providing good evidence that the potassium alkoxide of

**Table 1** Synthesis of (*E*)-α,β-unsaturated amides **3a–h**

| Entry | Aldolate | R | $R_1$ | Product | d.e.[a] | % Yield[b] |
|---|---|---|---|---|---|---|
| 1 | **2a** | Me | Ph | **3a** | >95 | 89 |
| 2 | **2b** | Me | Et | **3b** | >95 | 67 |
| 3 | **2c** | $PhCH_2$– | $Me(CH_2)_6$– | **3c** | 92 | 99 |
| 4 | **2d** | $^i$Pr | cyclohexyl | **3d** | 93 | 76 |
| 5 | **2e** | $^i$Pr | (*E*)-Ph(CH=CH)– | **3e** | >95 | 95 |
| 6 | **2f** | $^i$Pr | Et | **3f** | >95 | 99 |
| 7 | **2g** | $^i$Pr | Ph | **3g** | 92 | 94 |
| 8 | **2h** | $^i$Pr | *p*-MeOPh– | **3h** | 90 | 79 |
| 9 | **2i** | Ph | Et | **3i** | >95 | 47 |

[a] All diastereoselectivities were determined *via* $^1$H NMR spectroscopic analysis (300 MHz) of the crude reaction product. [b] Yields are for pure (*E*)-diastereoisomers isolated after chromatographic purification.




**Scheme 1** *Reagents and conditions:* (i) 9-BBNTf, $^iPr_2NEt$, $CH_2Cl_2$, 0 → −78 °C; $R_1CHO$, $CH_2Cl_2$; (ii) KHMDS (1.5 eq.), THF, −78 °C.

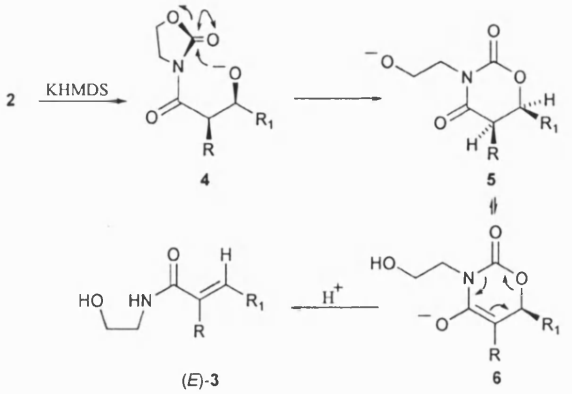
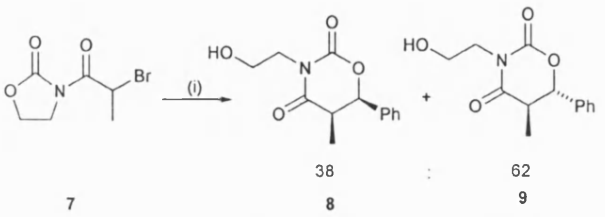


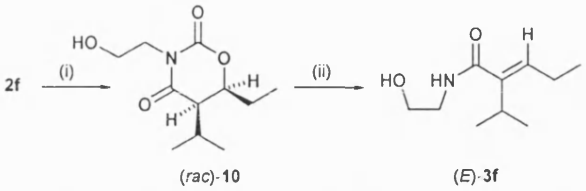

**Fig. 1** Intramolecular cyclisation/elimination mechanism for the formation of (*E*)-α,β-unsaturated amides **3**.

† Electronic supplementary information (ESI) available: synthesis and spectroscopic details for compounds **3a** and **12a**. See http://www.rsc.org/suppdata/cc/b3/b304213h/

DOI: 10.1039/b304213h



**Scheme 2** *Reagents and conditions:* (i) Zn, THF, −78 °C, PhCHO.

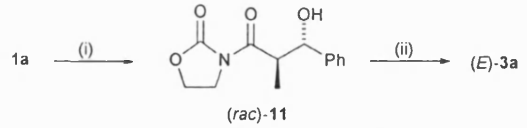


**Scheme 3** *Reagents and conditions:* (i) $Et_2Zn$ (10 mol%), $CH_2Cl_2$, 0 °C; (ii) KHMDS, THF, −78 °C.

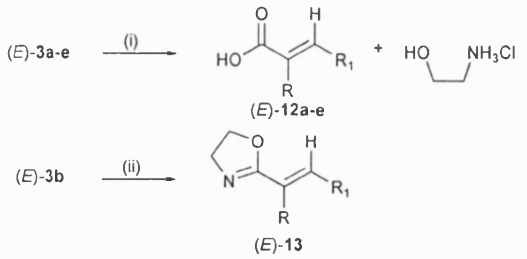
1,3-oxazinane-2,4-dione **5** is a key intermediate in controlling diastereoselectivity during stereoselective elimination of the potassium alkoxides of *syn*-aldolates **2a–h** (Scheme 3).

We next explored elimination of the corresponding *anti*-aldolate **11** which was prepared *via* treatment of **1a** with $MgCl_2$, TMSCl, $Et_3N$ and benzaldehyde in EtOAc according to Evans' recently published procedure.[13] Treatment of *anti*-aldolate **11** with KHMDS in THF at −78 °C afforded amide (*E*)-**3a** in >95% d.e. identical to that observed previously for elimination of *syn*-**2a** under the same conditions (Scheme 4). This is consistent with the key elimination step of both *syn*-**2a** and *anti*-**11** occurring *via* an E1cB-type mechanism, to afford a common enolate intermediate **6** that decomposes to afford α,β-unsaturated amide (*E*)-**3a** in high d.e.

In order to demonstrate the synthetic utility of this methodology, a range of diastereomerically pure trisubstituted secondary amides (*E*)-**3a–e** were hydrolysed to their parent acids **12a–e** by refluxing in 6 M HCl for two hours in 91–99% yield.† Importantly, no evidence of any products resulting from double bond migration were observed in the $^1H$ NMR spectra of the crude hydrolysis products of **3a–e** (Scheme 5, Table 2, entries 1–5).[14] The potential synthetic versatility of this methodology arising from the presence of the *N*-hydroxyalkyl substituent of α,β-unsaturated amides **3a–e** was also demonstrated *via*



**Scheme 4** *Reagents and conditions:* (i) $MgCl_2$, $Et_3N$, TMSCl, PhCHO, EtOAc, rt; (ii) KHMDS, THF, −78 °C.



**Scheme 5** *Reagents and conditions:* (i) 6 M HCl, Δ; (ii) $SOCl_2$, rt.

**Table 2** Yields of (*E*)-α,β-unsaturated acids **12a–e** and (*E*)-oxazoline **13**

| Entry | Amide | R | $R_1$ | Product | % Yield |
|---|---|---|---|---|---|
| 1 | **3a** | Me | Ph | **12a** | 99 |
| 2 | **3b** | Me | Et | **12b** | 91 |
| 3 | **3c** | $PhCH_2$– | $Me(CH_2)_6$– | **12c** | 99 |
| 4 | **3d** | $^i$Pr | cyclohexyl | **12d** | 99 |
| 5 | **3e** | $^i$Pr | (*E*)-Ph(CH=CH)– | **12e** | 99 |
| 6 | **3b** | Me | Et | **13** | 88 |

conversion of **3b** to its corresponding trisubstituted-α,β-unsaturated oxazoline (*E*)-**13** on treatment with thionyl chloride in 88% yield (Scheme 5, Table 2, entry 6).[15]

In conclusion, we have demonstrated that treatment of easily prepared *N*-acyloxazolidone-*syn*-aldolates with KHMDS affords an alkoxide intermediate which undergoes a stereoselective base mediated elimination reaction to afford trisubstituted (*E*)-α,β-unsaturated amides in high d.e.

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## Notes and references

1 For a recent review on the synthesis of carboxylic acids and esters see A. S. Franklin, *J. Chem. Soc., Perkin Trans. 1.*, 1999, 3537 and references therein.

2 (*a*) For examples see S. G. Davies, O. Ichihara and I. A. S. Walters, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1141; (*b*) M-J. Villa and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1569.

3 (*a*) For recent examples using Wittig methodology see R. J. Anderson, J. E. Coleman, E. Priers and D. J. Wallace, *Tetrahedron Lett.*, 1997, **38**, 317; (*b*) A. B. Smith III and B. M. Brandt, *Org. Lett.*, 2001, **3**, 1685.

4 For recent examples using Horner–Emmons methodology see (*a*) M. B. Andrus, E. L. Meredith, B. L. Simmons, B. B. V. Soma and E. J. Hicken, *Org. Lett.*, 2002, **4**, 3549; (*b*) Y. Hayashi, J. Kanayama, J. Yamaguchi and M. Shoji, *J. Org. Chem.*, 2002, **67**, 9443.

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8 Treatment of (*E*)-**2a** in THF with KHMDS at 0 °C afforded amide (*E*)-**3a** in an inferior 80% d.e.

9 The (*E*)-stereochemistry of amide **3d** was confirmed *via* X-ray crystallographic analysis.

10 For further discussion see (*a*) S. D. Bull, S. G. Davies, S. Jones and H. J. Sanganee, *J. Chem. Soc., Perkin Trans. 1*, 1999, 387; (*b*) S. P. Bew, S. D. Bull, S. G. Davies, E. D. Savory and D. J. Watkin, *Tetrahedron*, 2002, **58**, 9387.

11 See Reference 11 in Y. Ito and S. Terashima, *Tetrahedron*, 1991, **47**, 2821.

12 For examples where metal enolates of α,α-disubstituted-*N*-acyloxazolidin-2-ones gave rearranged 1,3-oxazinane-2,4-diones see (*a*) A. S. Kende, K. Kawamura and M. J. Orwat, *Tetrahedron Lett.*, 1989, **30**, 5821; (*b*) T. Kamino, Y. Murata, N. Kawai, S. Hosokawa and S. Kobayashi, *Tetrahedron Lett.*, 2001, **42**, 5249.

13 D. A. Evans, J. S. Tedrow, J. T. Shaw and C. W. Downey, *J. Am. Chem. Soc.*, 2002, **124**, 392.

14 For an alternative five step synthesis of acid (*E*)-**12a** from a chiral *N*-acyl-oxazolidin-2-one-*syn*-aldolate see J. Palaty and F. S. Abbott, *J. Med. Chem.*, 1995, **38**, 3398.

15 (*a*) Oxazolines are easily converted into their corresponding acids, esters, aldehydes or alcohols; see J. A. Frump, *Chem. Rev.*, 1971, **71**, 483; (*b*) A. I. Meyers, R. J. Himmelsbach and M. Reuman, *J. Org. Chem.*, 1983, **48**, 4053.